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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

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BULLETIN OF
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AUGUST 1948

MODERN TREATMENT OF PULMONARY SUPPURATION*

WILLIAM DEWITT ANDRUS

Professor of Clinical Surgery
Cornell University Medical College, New York, New York

By suppurative disease of the lung is meant an infection of the pulmonary parenchyma distinct from the ordinary pneumonias in which a variety of pyogenic organisms as well as the anaerobes of the mouth, notably the spirochaetes and fusiform bacilli, usually take part.

Pulmonary suppuration as the term is usually applied begins as a process pathologically different from pneumonia since all the structures to be found in a given part of the lung are involved. Thus, while in lobar pneumonia only the lumina of the alveoli are involved, in the pneumonitis in which some of the anaerobic mouth organisms participate, the bronchial walls, interstitial tissues, alveolar walls and even the blood vessels may be massively invaded and filled with the products of an intense inflammatory reaction. Moreover, while resolution is the rule in the various pneumonias and without apparent structural damage, the result of pneumonitis is at best a dense fibrotic scarring of the site and at worst the complete destruction of a large portion of the lung by

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gangrene. This process begins almost always as either a localized area going on to abscess formation or as bronchiectasis, but since unless eradicated completely both these processes tend to undergo recurrent exacerbations, many of the cases of pulmonary suppuration are seen in the later stages and when the pathological changes are far advanced.

Bronchiectasis. Although there may be a considerable amount of variation in the anatomical findings in bronchiectasis, the basic therapeutic problem is much the same in all and is so often best handled by surgical measures that this should be considered as the definitive treatment in all cases, although it may for various reasons be withheld in some. A patient with the characteristic findings of bronchiectasis has a serious condition which is apt to become progressively worse and which carries both a high morbidity and mortality rate. Such patients are prone to develop "pneumonia"—in reality an exacerbation of the basic suppurative process described above—which through recurrences may virtually incapacitate an adult so far as work is concerned and may seriously interfere with the normal growth and education of a child or adolescent.

The diagnosis of bronchiectasis is not difficult, and the demonstration of its extent by carefully performed bronchogram is usually quite successful. It is necessary, however, to be suspicious of its presence whenever a child or adult suffers from repeated chest colds or when a patient has a so-called unresolved pneumonia.

While the etiology of bronchiectasis is still obscure, it would appear that protracted cough or narrowing of the air passages such as is commonly seen in asthma, allergic bronchitis, or in bronchial stenosis from other causes may be definite contributory factors. The upper respiratory tract may be of importance both as a source of the initial infection, and when chronic or acute sinusitis is present may be responsible for repeated recrudescence of the pneumonitis. Elimination or curtailing of these upper respiratory infections is a most important part of the therapy. This becomes more obviously vital when we realize that it can be shown that in many patients with pulmonary suppuration the pharyngeal reflexes are quite sluggish—indeed, some like the gag reflex may be completely absent.

Most cases of bronchiectasis if they are to be handled conservatively really require a sanitarium type of regimen, including general hygienic measures, ample diet and attention to anemia if present. Elimination if

possible of specific sensitivities is advisable in the early stages and the modern anti-histamine drugs such as benadryl, pyribenzamine, etc., may be useful in diminishing the bronchial secretions which early, as an allergic reaction, may contribute to the development of bronchial obstruction and thus participate in the pathogenesis of bronchiectasis. In the later stages, however, little is to be expected from desensitizing, nor in the presence of actual pulmonary suppuration from these specific drugs.

All of us remember the time when the various arsenicals were employed in the hope of controlling the spirochaetes in such infections, and the disappointment which followed. In most welcome contrast, however, is the use of penicillin, particularly in controlling certain of the flora involved in pulmonary suppuration. While it cannot be considered as curative in the established case of bronchiectasis since here irreversible changes in the bronchial wall have already taken place, it is a most vital ancillary method in the control of reinfection and the prevention of further damage. Its administration by aerosol has the advantage of bringing the drug in more direct contact with the intrabronchial infection and, as it is absorbed, of producing a systemic effect as well. It has been shown repeatedly that satisfactory blood levels can be produced after inhalation even though larger doses may be required than by the intramuscular route. The so-called vaponefrin nebulizer which produces very small droplets is the most satisfactory method of administration and the dosage recommended by those with the most experience is from 150,000 to 500,000 units made up in physiological saline 50,000 U/cc. from crystalline penicillin and given in three to five inhalations q.d. Such treatment may be expected to produce moderate to marked improvement in about two-thirds of the cases, with disappearance of many gram-positive organisms, but as with the systemic administration of penicillin, relapse is common. It would seem wise, however, in view of the known high incidence of re-exacerbation of both bronchiectasis and lung abscess in the presence of acute upper respiratory infection to initiate such treatment at the first signs of a cold, not with the idea of controlling the virus but of preventing the rekindling of the intrapulmonary process.

In the absence of facilities for aerosol administration, the systemic route may be used where a dosage of 25,000 U. q. 3 hours or of 300,000 U in oil once or twice a day may be expected to bring about

some improvement in the majority of cases. It should be emphasized that penicillin alone seldom if ever cures established bronchiectasis.

When Friedländer's bacillus or gram-negative organisms are present, streptomycin, 0.5 gm. T.I.D., may also be employed with benefit.

Since conservative local measures have as their purpose the elimination of the purulent bronchial secretion by coughing, medication aimed at checking the cough may be harmful while those that promote expectoration are beneficial. The chief conservative measure in the treatment is postural drainage, one of the oldest but still applicable. Many patients are able to select the position best suited for drainage in their own cases, but because of the prevalence of the process in the lower lobes the most satisfactory method is to have the patient lie prone across the bed with the hands on the floor or over the lower part of a hospital bed in which the portion normally supporting the knees has been angulated sharply upward. In some instances patients tolerate this very well and can even sleep in this position. Postural drainage finds its chief usefulness as a preparation for surgery and as a definitive measure in those cases in which because of extensive bilateral involvement or for other reasons operation is inadvisable.

Bronchoscopy should be carried out in all cases, if only to rule out the presence of foreign body or bronchial stenosis, benign or malignant, as possible etiological factors. Aspiration of secretions, and particularly those retained behind piled up granulation tissue, may be possible after the local application of vasoconstrictor drugs. Bronchoscopy should usually be withheld, however, in the presence of surrounding pneumonitis since it is apt to be followed by untoward reactions under such circumstances.

It is now generally accepted that the definitive treatment of bronchiectasis is surgical unless certain contraindications such as the general condition of the patient or the too extensive involvement of both lungs makes surgery impossible. Established bronchiectasis is a serious disease, and Perry and King[1] in following 400 patients showed that over a 12-year period the mortality in the non-surgically treated cases was 26 per cent. Of these who died, 41 per cent did so within five years of the recognized onset of the disease, and only 15 per cent lived more than twenty years. It is of further interest that of the persons developing the disease under ten years of age, only 9 per cent lived to be over forty and in only 15 per cent of the patients in the larger series who

were over forty did the disease begin in the first decade.

Bradshaw, Putney and Clerf[2] found that among a group of 171 patients who could be followed out of a larger series of 242, 112 were living and 59, or 24.5 per cent, had died of bronchiectasis or its complications. Riggins[3] reported a 14 per cent mortality in his series of 85 cases, and Hinshaw and Schmidt[4] in summarizing various series found that less than 10 per cent of the cases of severe bronchiectasis obtained a satisfactory result from any form of medical treatment. They believe the mortality rate within ten or fifteen years after the disease is discovered to be 30 to 50 per cent.

These figures seem high, and yet the best of them are so far inferior to those following surgery as to make indefinite medical treatment and the withholding of surgical intervention a highly questionable procedure in the absence of very excellent reasons. This is particularly true since the advent of penicillin makes possible the prevention of complications such as empyema and sepsis which were responsible for much of the earlier mortality. All the other surgical measures which were formerly employed such as pneumothorax, phrenicotomy, thoracoplasty, pneumonostomy and so-called cautery pneumonectomy have now been abandoned, leaving the field to lobectomy and pneumonectomy.

Lobectomy or pneumonectomy for bronchiectasis as now practised with adequate pre-operative preparation and postoperative care has lost most of its dangers, and patients who survive the operation are more nearly cured and need not fear recrudescence of the disease when all demonstrable bronchiectasis has been eliminated.

The preparation of such patients for operation involves first the accurate delineation of the site and extent of the process, recognizing that while most often to be found in the lower lobes, the middle lobe on the right and its analogue, the lingula of the left upper lobe, are commonly involved either alone or in conjunction with disease in the lower lobes. The indications for surgery in bronchiectasis so far as the sites of involvement are concerned may be summed up by considering it the treatment of choice for those cases in which the disease is restricted to one lobe only, to the right lower and middle lobes, and to the left lower and the lingula of the left upper. In some cases it is also indicated where all lobes of one lung or one lobe of each lung, or two lobes of one lung and one of the other are involved. Severe or continued hemoptysis is an urgent indication for surgical intervention

provided the source of the bleeding can be identified, though in bilateral disease this may be difficult even after bronchoscopy.

All patients should have adequate postural drainage for several days before operation, and a thorough attempt should be made by this method to clear the bronchial tree immediately before beginning anesthesia. General anesthesia with intratracheal intubation to permit frequent aspiration of secretions and with that type of agent which will permit the cough reflexes to be most promptly re-established is the method of choice. Our own preference is for pentothal induction, followed by cyclopropane.

The technique of intrahilar dissection with individual ligation of the structures is much to be preferred over the older mass ligation or tourniquet methods, but in certain cases in which the hilus is "frozen" because of fibrotic reaction may not be feasible. When possible, however, it should be carried out as it reduces materially the dangers of complicating empyema and bronchial fistula. The stump in any case should be covered with pleura either by a flap from the operative area or a free graft taken from the chest wall or elsewhere. Transfusion on the operating table should be provided as for any major operative procedure.

The courageous attempts at eradication of bronchiectasis by lobectomy of Lillienthal, Heuer, Sauerbruch, Willy Meyer, and others were attended by a frightful mortality, but thanks to their efforts and those of others, as well as to the advances in the general care of patients before and after major surgical procedures, the risk of lobectomy for bronchiectasis is now materially reduced. Thus, the operative mortality in some of the more recent and larger series is as follows: Churchill in 116 patients had a mortality of 3 per cent; Bradshaw and O'Neil,[5] 24 patients with one death—4 per cent; Maier,[6] 64 cases with one death—1.6 per cent; and finally in a series from a single Army hospital in this country[7] in which to be sure the risks may have been somewhat lower due to the pre-induction screening, 196 lobectomies were performed for this condition with one death. The overall mortality of lobectomy in this condition is therefore well below 5 per cent in competent hands.

When more than one lobe and particularly because of the multiple operations required when more than one side is involved, the risk is definitely greater, but in an otherwise uncomplicated case even this

does not compare with that of an indefinite conservative policy. When both sides are affected, operation is attended by an additional risk in that the patient's convalescence after the first procedure must be carried out in the presence of the remaining existing disease.

Postoperatively such patients receive the care given any major thoracotomy—transfusions, oxygen tent as needed, and the retention of the closed drainage tube inserted at operation so long as it continues to function.

Lung Abscess. A lung abscess begins as a localized area of pneumonitis caused by the varied flora mentioned above, and among which the mouth anaerobes may usually be found. It is not necessary to go into the known facts regarding its etiology nor to discuss the polemic which has raged in the past regarding the route whereby the infecting organisms reach the lung. It is to be hoped, however, that the large proportion of the lung abscesses which formerly followed operations about the nose and throat may be reduced in number through the prophylactic use of penicillin before and after such procedures.

In considering the modern treatment of lung abscesses it should be borne in mind that the final healing of any abscess regardless of site or etiology is accomplished through the fulfillment of three processes which, while they may progress concurrently, are all significant. These are drainage or evacuation of the abscess cavity, its sterilization and finally its obliteration. Applying this to the lung abscess we find that in the early stages if access to the bronchus be sufficient to provide adequate and prompt drainage, the normal body defenses may overcome the infection and the walls of the cavity may collapse to produce its obliteration. As the infection persists, however, the tissue reaction, particularly to certain of the mouth organisms, produces an increasingly dense, fibrous wall which makes collapse more and more difficult. Persistence of the infection may be due in a few instances to a retained foreign body, but is more often caused by poor drainage, and this in turn through blockage of the tributary bronchus by edema, granulation tissue or in some cases by tumor. It is estimated that in from 20 to 35 per cent of lung abscesses the normal processes outlined above will bring about cure, but the remainder show a great tendency to chronicity and it is difficult to determine, except on the basis of large experience and then guardedly, when the natural tendency to healing ceases and the trend to chronicity becomes established. Realization of this fact

long ago led certain surgeons, notably Dr. Harold Neuhof[8] and Dr. George Heuer,[9] to adopt a more aggressive attitude toward the surgical drainage of lung abscess, and since the advent of modern antibiotic therapy has reduced its complications in this condition, this attitude is now fairly well accepted as correct. While some are more radical and some less so, most experienced thoracic surgeons now adopt the policy that if signs of spontaneous healing such as diminution of fever, cough and sputum and decrease of the size of the shadow in the x-ray both as it relates to surrounding parenchymal reaction and to the size of the cavity itself are not apparent after two or three weeks of conservative therapy, surgical intervention should be undertaken.

The conservative measures used in the treatment of lung abscess are essentially the same as those employed in bronchiectasis, except that in its initial stages the process may be more acute in the former. Postural drainage, intensive antibiotic therapy and bronchoscopy all find a place in the conservative regimen and have about the same limitations here as in bronchiectasis. The early cases treated by penicillin alone in our own series and that of others demonstrated its usefulness in controlling the spread of pneumonitis and causing the anaerobes and certain other organisms to disappear from the sputum and in bringing about a marked decrease in size of the cavity. As this failed to be completely obliterated, however, re-exacerbation promptly occurred when the penicillin was stopped.

Mention should be made here of abscesses yielding Friedländer bacillus and microaerophilic streptococci, the first of which is usually and the latter often insensitive to penicillin, so that a more radical attitude is advisable from the start. Streptomycin may help to eradicate the Friedländer infection, but control of this streptococcus may be exceedingly difficult. This latter organism in our experience often gives rise to multiple lung abscesses and to associated putrid empyema, and these facts when taken with its frequent resistance to antibiotics makes treatment difficult. Here, particularly, early surgical attack on the abscess is desirable.

The modern treatment of lung abscess seen very early in its course may then be said to consist of conservative measures, including postural drainage, intensive antibiotic therapy and bronchoscopy as indicated, for no longer than from two to four weeks at most, unless the process shows very satisfactory evidence of resolution. Even with such evi-

dence, however, the cavity should be followed to complete obliteration, and if conservative measures alone are used, the patient should be kept on what amounts to a sanitarium regimen, including rest, general hygienic measures and meticulous protection against upper respiratory infections for several months. If not evidently successful in producing a satisfactory trend toward healing, conservative measures should be replaced by surgery—in this case drainage in one or two stages as the circumstances and the experience of the surgeon require.

By such means today uncomplicated lung abscesses can be healed in a far greater number than formerly, but unfortunately many if not most are not yet being treated as early or as vigorously as this ideal regimen would require. Either the abscess is not recognized and hence the treatment is begun relatively late, or if started early conservative measures are continued so long that a complete obliteration of the cavity is not obtained and a chronic abscess is the result.

Chronic lung abscess is characterized not only by the thickened fibrous wall already commented upon, but often by the honey-combing of the surrounding lung parenchyma with other abscesses, the result of repeated spread of the infection. Under such circumstances adequate drainage either via the bronchial tree or to the exterior is practically out of the question and surgical extirpation of the involved lung becomes the only alternative. This procedure was formerly accompanied by a high mortality as it usually has to be done in a debilitated patient, but by the use of general supportive measures, antibiotic therapy and technical advances in the removal of such tissue, one of the brightest chapters in pulmonary surgery is being written.

Since in chronic lung abscess only a portion of a lobe is usually involved, the operation commonly employed is segmental lobectomy. In this procedure the bronchus and vessels to the involved segment are divided and ligated near the hilus and only the portion of pulmonary parenchyma removed which is supplied by that bronchus. In this way, neighboring segments of two lobes may be removed if involved, thereby sparing a considerable amount of normal pulmonary tissue. Just as a more radical attitude toward early surgical drainage in suitable cases of acute lung abscess has given demonstrably better results, so the use of segmental lobectomy or even complete lobectomy when indicated is bringing about the cure of chronic abscesses and without the prolonged hospitalization which was the best that could previously

have been hoped for. Such extirpation has the advantage also of identifying a malignancy if present and permitting such additional surgery as may be indicated to be undertaken promptly.

As stated earlier, pulmonary suppuration is a serious condition and one may add that it often presents a complicated problem in therapy, but as I hope I have been able to point out, really significant strides are now being made in improving the results. Because of the variegated picture which may be presented both as regards the extent and severity of the lesions in individual cases, more data must be accumulated before the complete significance of the newer methods can be evaluated. In the meantime, the prompt application of the methods now available to each case and the close co-operation of those responsible for their carrying out in following their results will assure the best results and the lowest incidence of complications.

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MEDICAL ASPECTS OF THROMBOPHLEBITIS*

EDGAR V. ALLEN

Division of Medicine, Mayo Clinic, Rochester, Minnesota

THE WORD thrombophlebitis implies occlusion of a vein by a thrombus, and inflammation of the vein itself. Actually the terms phlebothrombosis, thrombophlebitis, and venous thrombosis may be considered synonyms in most instances. While I am aware that some clinicians identify phlebothrombosis as a separate entity from thrombophlebitis, it has been my experience, ordinarily, that I could not accomplish this. Actually differentiation is of insignificant importance. The clinician cannot depend upon a diagnosis of thrombophlebitis to relieve his mind of the fear of pulmonary embolism which is believed to occur less frequently where there is "phlebitis" than where there is only venous thrombosis. These brief statements do not deny that there are two pathologic entities, venous thrombosis with phlebitis and venous thrombosis without phlebitis. They only deny that one can differentiate the two conditions by clinical means in many instances, and they deny that such differentiation would be important ordinarily, even if it were possible. Therefore, we may dispense with confusion in this presentation by considering synonymous the terms, phlebothrombosis, thrombophlebitis and venous thrombosis. For the sake of clarity I shall use the term thrombophlebitis to include all of them.

In general there are two causes of thrombophlebitis, injury to vein wall and changes in the blood. An example of injury to the vein wall is the thrombophlebitis which follows the intravenous injection of irritating solutions such as a hypertonic solution of sodium chloride. An example of thrombophlebitis secondary to changes in the blood is that occurring in polycythemia vera. Actually these statements oversimplify the problem. There are many instances of thrombophlebitis for which the mechanism is not readily apparent. For example, what causes thrombophlebitis following an abdominal operation? Our studies indicate

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clearly that blood flows more slowly in the veins after operation but we do not know that this slowing of flow causes thrombophlebitis. What causes superficial thrombophlebitis of patients who have cancer of the lung, stomach or pancreas? Do these lesions release noxious substances into the blood which provoke thrombophlebitis? There is no answer to these questions.

Moreover there exists considerable uncertainty relative to the diagnosis of thrombophlebitis at times. There is of course no difficulty when a superficial vein has been transformed into a hard inflamed subcutaneous cord or when an entire limb rather quickly becomes edematous and there is visible evidence of collateral venous circulation. But what is one to conclude when a patient who has had a major abdominal operation complains of soreness in the calf? On examination there may be only slight tenderness to pressure over the calf muscles or on dorsi-flexion at the ankle. Does the patient have thrombophlebitis? We presume so, but usually we have no proof. There was hope, for some time, that phlebography might permit an answer to the question just asked. Actually it has limited value in such cases.

It is beyond the scope of this presentation to consider all the kinds of thrombophlebitis. There is no very good classification either on etiologic, geographic or clinical grounds. It is probably wise in this consideration to omit the rare conditions which are extensively considered elsewhere, and consider the more common. Also, it seems wise to try to express a process of thinking when one sees a patient with thrombophlebitis. Perhaps this is best done with questions and answers as follows.

Question—When a physician sees a patient with superficial thrombophlebitis what should he consider to be the cause? Answer—He should determine first whether the vein has been injured by trauma or injection. He should consider phlebitis in varices, for phlebitis occurs commonly in varicose veins probably as a result of destruction of intima, slowing of blood flow and reduced oxygen saturation of blood. He should consider thrombo-angiitis obliterans because superficial thrombophlebitis occurs at some time in the course of 40 per cent of patients with thrombo-angiitis obliterans. When it occurs there is usually also evidence of occlusive arterial disease but thrombophlebitis may precede the clinical evidence of arteritis for many years. The physician must think of polycythemia vera which notoriously provokes both arterial and

venous occlusion. He must think of malignancy, inasmuch as carcinoma of the bronchus, stomach and pancreas is not infrequently the direct cause of venous thrombosis. There may be failure of clinical evidence of malignancy in these areas at this time but at a later date there may be clinical, surgical or anatomic evidence of carcinoma. Lymphoblastoma may also cause superficial phlebitis. Finally, superficial thrombophlebitis may occur without apparent cause; the situation is comparable to tonsillitis, appendicitis and cholecystitis except that a bacterial cause is not commonly apparent in phlebitis.

The treatment of superficial thrombophlebitis is of course the treatment of the cause of it, when that can be determined. Superficial phlebitis itself may require no specific treatment. Indeed, the commonest type of superficial venous thrombosis, that following injection treatment of varices is ordinarily given no specific treatment. It is surprising how inconsistent we are in our attitude toward two kinds of phlebitis in varices, that caused by injection of a sclerosing solution and that occurring spontaneously. When the phlebitis is intentionally provoked the patient is kept active. When phlebitis occurs spontaneously in varices it has been customary to restrict the patient to bed. There is no satisfactory explanation of this inconsistency. One is quite certain that the clot is firmly anchored to the wall in chemical thrombophlebitis; he is not so certain when thrombosis occurs in varices spontaneously. However, pulmonary embolism from superficial thrombophlebitis is very rare.

There are two aspects of superficial phlebitis which deserve special consideration and care. If the thrombosis progresses close to the juncture of the greater or lesser saphenous systems with the femoral or popliteal veins respectively, its progress must be halted either by anticoagulants or by surgical ligation and division. To fail to halt the process of thrombosis may permit extension of it into the femoral or popliteal vein from which it may become detached to cause pulmonary embolism. The second aspect is the possibility of thrombophlebitis of the deep veins associated with superficial phlebitis. If any evidence of this exists it is well to use anticoagulants.

About what should a physician think when he sees a patient with deep thrombophlebitis? Naturally he should think first of the cause of which the three most common are operation, delivery and bed rest as a result of illness of a medical nature. It may result from trauma, from many infectious diseases as, for example, pneumonia and tularemia, from

polycythemia or leukemia or from pregnancy. If none of these or malignancy or thrombo-angiitis obliterans are apparent on careful examination the physician will need to consider that the thrombophlebitis of the deep veins is of the "idiopathic" type.

One treatment of deep thrombophlebitis is, of course, the treatment of its cause if that can be determined. However, there is need for immediate treatment of deep thrombophlebitis, first to prevent pulmonary embolism, second, to restrict the thrombosis to as small an extent as possible in order to lessen as much as possible the chronic venous insufficiency which is an inevitable consequence of venous thrombosis. It manifests itself after recovery of the acute episode by edema, varices, stasis dermatitis and stasis ulceration.

In addition, we are becoming increasingly more aware of the syndrome of acute peripheral circulatory failure, that is, shock, associated with acute venous thrombosis of a leg. We have noted clinically a number of cases of acute venous thrombosis without pulmonary embolism, which have been characterized by cold ashen moist skin, tachycardia, blood pressure which is low or cannot be determined and transitory azotemia; all of the peripheral arteries may be pulseless and anemia may follow the episode. We have as yet, not made essential studies of circulating blood volume but there is clinical evidence of shock similar to that resulting from hemorrhage. We have not measured the actual increase in the volume of a limb affected with acute venous thrombosis but our estimations indicate that large amounts of fluid, perhaps as much as six to ten liters may be trapped in a limb. The syndrome of shock is probably related to the extent and speed of the swelling of the limb. A limb which is rather quickly and progressively involved with venous thrombosis may swell markedly and thus draw from the general circulation a large amount of blood and water. We are not certain that this syndrome, if untreated, would of itself cause death of the patient but that is a possibility. Certainly every patient with acute venous thrombosis should be observed for signs of peripheral circulatory failure. Transfusion may be indicated to restore the circulating blood volume. The entire subject needs careful study. Currently it can be said only to be provocative.

I have arrived now, somewhat circuitously, to the topic of active treatment of thrombophlebitis. It is unfortunate that there is no surgeon to present the case for ligation of veins. I don't believe that indicates

there is no case for ligation of veins. However, I wish to dismiss it with a few sentences. I believe that anticoagulants will do as much or more for patients with thrombophlebitis as ligation of veins will. I prefer anticoagulants to ligation of veins in all cases except when anticoagulants are contraindicated, and when they have not been effective. It is unfortunate, too, that some surgeon or anesthesiologist is not here to present the case for anesthetization of appropriate sympathetic ganglia. I am aware of the statements that this procedure lessens pain, fever, and edema in acute venous thrombosis. In my experience, with rare exceptions, the pain of acute phlebitis requires only aspirin or codeine. Fever is usually mild and certainly not harmful. I have observed little or no effect of anesthetization of sympathetic ganglia on edema. The statement that this procedure lessens the remote consequences of acute venous thrombosis, that is chronic venous insufficiency, seems on very insecure footing. I wish it could be proved to be true. Finally, I believe that elevation of the extremity and the application of warm moist packs has the same physiologic effect on circulation of a limb as sympathetic block and is to be preferred because of its simplicity.

The contribution to the treatment of thrombophlebitis which is of the greatest interest now is treatment with the anticoagulants heparin and dicumarol

Dicumarol is a pure chemical compound which may be recovered from spoiled sweet clover and which has been prepared synthetically. The discovery that it is the agent which causes spoiled sweet clover disease of animals which is characterized by hemorrhage, the determination of its chemical formula, the synthesis of it and other studies by Link and his associates mark an epoch in research which is admirably presented in the Harvey Lectures for 1943-1944. Dicumarol impairs coagulation of the blood, in vivo, by depressing the values for prothrombin. When used clinically it has no other significant effect, except that hemorrhage may result when the concentration of prothrombin in the blood is diminished too greatly. Dicumarol is not an ideal anticoagulant because its effect is delayed for one to two days after oral administration, because its effect persists for several days after discontinuance of administration and because judicious use requires the services of skilled and experienced laboratory personnel. Heparin, the only other anticoagulant available for clinical use, has the advantage of quick action (within a few minutes after intravenous injection) and quick cessation of action

(about three hours after injection). A further advantage is that it can be satisfactorily administered without "laboratory control." The disadvantages of use of heparin are the relatively great cost and the need for parenteral administration.

Heparin and dicumarol are not competitors for clinical use; the use of one complements the use of the other. In many instances they should be used together. Heparin should always be used when an anticoagulant effect is needed quickly and when reliable laboratory determination of the value for prothrombin in the blood is not available. Although it may be given by continuous administration, the intravenous injection of 50 mg. of heparin (5 cc. of solution) every four hours has been satisfactory for clinical use. Dicumarol should be used whenever an anticoagulant effect is needed over a period of days, weeks, months or years, provided that there are available reliable determinations of the value for prothrombin in the blood. When both a rapid and a prolonged effect of an anticoagulant are desired, heparin and dicumarol should be administered simultaneously; administration of heparin should be discontinued when dicumarol has produced a satisfactory effect on prothrombin.*

The Dosage of Dicumarol. The amount of dicumarol to be used depends entirely on the value for prothrombin in the blood after the drug has been administered on two successive days. In our studies we have attempted to maintain the values for prothrombin in the blood between 10 per cent and 30 per cent, since our experiences have indicated that significant hemorrhage seldom occurs when the value for prothrombin in the blood is more than 10 per cent and that intravascular thrombosis seldom occurs when the value for prothrombin is less than 30 per cent. It is possible that dicumarol may be administered with satisfactory results if the value for prothrombin in the blood is not reduced as much as we have indicated.

The inexperienced may be confused by the use of the terms "prothrombin time" and "prothrombin percentage"; they do not have the same significance nor do they have a linear relationship. The laboratory should furnish to the clinician a chart by means of which he may convert prothrombin time into prothrombin percentage. According to the technique used at the Mayo Clinic, a normal prothrombin time is 17 to 19 seconds; a prothrombin time of 27 seconds signifies 30 per cent

* When both heparin and dicumarol are used, blood for determination of the values for prothrombin should be drawn not less than three hours after the last injection of heparin, since heparin itself modifies the result of the test for prothrombin.

prothrombin; 35 seconds signifies 20 per cent prothrombin and 58 seconds indicates 10 per cent prothrombin. However, in other institutions where different thromboplastins or techniques are used in the performance of the prothrombin time test, quite different prothrombin times may correspond to values for 100 per cent, 30 per cent, 20 per cent and 10 per cent prothrombin.

Three hundred milligrams of dicumarol are given on the first day and 200 mg. on the second day. On each subsequent day when the prothrombin is more than 20 per cent, 200 mg. are given. On any day when the value for prothrombin is less than 20 per cent, dicumarol is withheld. There are minor variations of this program depending on sensitivity or resistance of a patient's prothrombin to dicumarol.

The Danger of Hemorrhage When Dicumarol Is Used. The sole danger associated with the use of dicumarol is hemorrhage. In our series of 1,983 postoperative cases minor hemorrhage (epistaxis, hematuria and localized ecchymosis) occurred in 3.4 per cent of cases and serious bleeding (from operative wounds or from the gastrointestinal tract) occurred in 1.8 per cent of cases. One may expect minor bleeding in about one of each 25 postoperative cases and serious bleeding in about one of each 50 postoperative cases. There is a great difference between serious bleeding and fatal bleeding. Although marked bleeding from operative wounds occurred about 40 times during the course of treatment of almost 2,000 patients who had undergone operation, death from hemorrhage occurred only twice. Careful study of the records of these two fatalities, reported in detail elsewhere, indicates that the fatal hemorrhage could not definitely be attributed to the effect of dicumarol. However, the two fatalities emphasize the ever-present danger of hemorrhage when dicumarol is used.

The Prevention and Control of Hemorrhage. The best method of preventing hemorrhage is to use dicumarol expertly. Even then, hemorrhage will occur. When epistaxis, hematuria and local ecchymosis are minor we do not ordinarily alter dosage but observe the patient for signs of more extensive bleeding. If bleeding from an operative wound is continued or marked, synthetic vitamin K (menadione bisulfite) should be administered intravenously in amounts of 60 mg. and transfusion of fresh blood should be used to restore the blood that has been lost. The injection of vitamin K can be repeated at two hour intervals, once or twice as needed.

TABLE I

RESULTS OF USE OF ANTICOAGULANTS IN 352 CASES OF POSTOPERATIVE VENOUS THROMBOSIS

	Cases	
	*Expected if Anticoagulants had not been used**	*Occurred*
Subsequent venous thrombosis or pulmonary embolism	88	9†
Fatal pulmonary embolism	20	0

* On the basis of the rates given in the reports of Barker, Nygaard, Walters and Priestley.

† In 3 cases the percentage of prothrombin in the blood was more than 30. In 1 case use of dicumarol had been discontinued and prothrombin was normal.

TABLE II

RESULTS OF PROPHYLACTIC USE OF DICUMAROL IN 832 CASES OF ABDOMINAL HYSTERECTOMY

	Cases	
	Expected if Anticoagulants had not been used	*Occurred*
Venous thrombosis or pulmonary embolism	33	3*
Fatal pulmonary embolism	6	0

* Minor venous thrombosis.

TABLE III

RESULTS OF ANTICOAGULANT THERAPY IN 329 CASES OF PULMONARY EMBOLISM

	Cases	
	Expected if Anticoagulants had not been used	*Occurred*
Subsequent venous thrombosis or pulmonary embolism	144	3
Fatal pulmonary embolism	60	1*

* Occurred after prothrombin time had returned to normal.

Contraindications to the Use of Dicumarol. We use dicumarol cautiously or refrain from its use in renal insufficiency, which prolongs and enhances the effect of dicumarol, after operations on the brain or spinal cord, because bleeding in these regions might result in disaster, in blood dyscrasias with increased tendency to bleed because dicumarol will accentuate the tendency to bleed, in ulcerative lesions because of the tendency to bleed, and in nutritional deficiencies or hepatic diseases associated with potential or actual prothrombin deficiency. We doubt whether the use of anticoagulants adds anything to the treatment of subacute bacterial endocarditis and we do not use them in such cases, since the danger of hemorrhage is relatively great.

*Experience in 2,019 Postoperative Cases.** The results of treatment in 352 cases of postoperative venous thrombosis are shown in Table I. In 832 cases of abdominal hysterectomy dicumarol was given prophylactically (Table II) because experience has indicated that in 4 per cent of such instances venous thrombosis occurs following operation; death from pulmonary embolism occurs in 0.7 per cent. In 329 cases of pulmonary embolism after operation anticoagulants were used (Table III). In addition to the cases considered in Tables I, II and III, there were 470 instances in which dicumarol was used prophylactically to prevent pulmonary embolism and venous thrombosis. These were instances in which venous thrombosis or pulmonary embolism had occurred after previous operations or in which the prospects of postoperative venous thrombosis were considered relatively great. Venous thrombosis occurred in two instances: There was no instance of pulmonary embolism.

In 36 additional cases dicumarol was used prophylactically after amputation of a leg because of arteriosclerosis obliterans or thromboangiitis obliterans; there were no vascular complications except that bleeding into the region of amputation occurred in one instance. Unfortunately no figures are available for comparison of results with and without anticoagulants. We can indicate only that dicumarol provided adequate protection against venous thrombosis in these cases.

An over-all consideration of the 1,513 cases presented in Tables I, II, and III indicates that the following results were achieved: 85 patients survived who might have been expected to die had anticoagulants not been used; 250 patients were spared venous thrombosis or non-fatal pul-

* In many instances of pulmonary embolism heparin and dicumarol were used. In most instances of venous thrombosis, dicumarol alone was used. In all instances in which an anticoagulant was used prophylactically, dicumarol only was used.

monary embolism. No great accuracy is claimed for these figures since alternate patients were not treated with and without anticoagulants; the control figures were calculated from experiences before anticoagulants were used. We recognize the deficiency in this method of study but the striking efficiency of anticoagulants in preventing pulmonary embolism and venous thrombosis is nonetheless impressive.

Additional Disadvantages of Anticoagulant Therapy. In considering venous thrombosis and pulmonary embolism there is one most desirable goal: absolute prevention. This has not been achieved. Table II illustrates the point well. Eight hundred thirty-two patients who had undergone abdominal hysterectomy were treated with dicumarol in order to save six lives and in order to prevent venous thrombosis and non-fatal pulmonary embolism in 30 instances. The returns might be considered small. The numerical results are more impressive in cases of venous thrombosis and non-fatal pulmonary embolism; yet it was necessary, in the aggregate, to treat 681 patients in order to save 79 lives and to prevent further venous thrombosis and embolism in 220 instances. We do not belittle these results. We only emphasize our inability to detect the predisposition to venous thrombosis *before it occurs.* Were it possible to designate the patients who would have venous thrombosis *before they had it,* treatment with anticoagulants would be even more productive. There has been a good deal of study on this phase of the problem of venous thrombosis and embolism; some progress has been made on the periphery but the hard core of the problem remains.

Anticoagulants in the Postpartum State. Previous reports indicate that dicumarol may be used safely and with benefit in the treatment and prevention of venous thrombosis following delivery. Indeed the first dose may be administered prophylactically during labor and administration may be continued during the postpartum state without inducing uterine hemorrhage. Dicumarol may appear in the milk of lactating animals to which it is given; indeed baby rats nursing from mothers receiving dicumarol may bleed and die. However, the dose (5 mg. daily) given to the mother rats produced prothrombin deficiency in their blood and caused them to die in six to nine days. The dose administered to the rats was many times greater than that given to patients, if body weight is considered. No conclusions can be drawn from these studies except that if rats are given excessive amounts of dicumarol, their milk may contain sufficient dicumarol to produce profound prothrombin defi-

ciency in nursing young. There is no clinical corollary to this situation.

We have administered heparin and dicumarol or dicumarol alone to 19 postpartum patients, four of whom had pulmonary embolism and 15 of whom had venous thrombosis in the legs. Four of these patients had undergone cesarean section. Treatment was begun as early as the fifth postpartum day to patients who had vaginal delivery and as early as the eleventh day following cesarean section. There was no unusual bleeding although the values for prothrombin in the blood were mostly between 10 per cent and 30 per cent after the third day of treatment. In no instance was there further venous thrombosis or pulmonary embolism. Only two mothers were nursing their babies while they received dicumarol. Repeated studies of the blood of each baby indicated that the values for prothrombin were never reduced significantly; they were consistently between 90 per cent of normal and normal, even when the values for prothrombin in their mothers' blood were between 10 per cent and 30 per cent.

Our studies support the conclusions of previously published reports that anticoagulants may be used after delivery, as needed for the prevention and treatment of pulmonary embolism and venous thrombosis. The problem of prothrombin deficiency of babies induced by dicumarol in mothers' milk cannot be considered wholly settled, although prothrombin deficiency did not occur in our two cases. When dicumarol is given to a mother who is nursing a baby, it is probably the course of wisdom to give the baby vitamin K or to determine values for prothrombin in the baby's blood and to correct any deficiency of prothrombin which may occur.

Experience with Medical Patients. A group of 288 patients who had various kinds of vascular diseases have been given dicumarol as part of their program of medical treatment.[1]

Thrombophlebitis.—In this group were 138 patients. The thrombophlebitis was of the idiopathic type (one episode) in 42 cases and of the re-recurrent idiopathic type (several episodes) in 27. In 16 cases the thrombophlebitis followed trauma, in eight it was associated with acute infections, in eight with carcinoma, in five with blood dyscrasias, in four with thrombo-angiitis obliterans and in 11 with miscellaneous conditions which may cause thrombophlebitis. In 17 cases the thrombophlebitis occurred in varices including incompetent greater and lesser saphenous systems.

In 90 cases the thrombophlebitis involved the iliofemoral or deep sural veins or both.

The chief reason for giving dicumarol was to prevent pulmonary embolism and further venous thrombosis. There is no reliable information available as to the incidence of subsequent pulmonary embolism or venous thrombosis among patients who have thrombophlebitis which does not follow operation but it is reasonable to assume that it may be about as high as in the group of patients who have iliofemoral or sural thrombophlebitis following operations.

In this group fatal pulmonary embolism did not occur; two patients had non-fatal pulmonary embolism during adequate prothrombin deficiency. In four cases subsequent venous thrombosis developed. In one of these cases it occurred after the administration of dicumarol had been discontinued because of difficulties in obtaining blood for prothrombin determinations and after the prothrombin value had returned to normal; in another the venous thrombosis occurred when the prothrombin value was greater than 30 per cent. In the two remaining cases there was adequate prothrombin deficiency at the time of the development of the venous thrombosis.

Pulmonary Embolism.—There were 44 patients in this group. The incidence of subsequent pulmonary embolism and venous thrombosis without anticoagulant therapy among medical patients who have iliofemoral or sural thrombophlebitis is unknown but it probably is the same as that noted among patients after operation. In the group of medical patients with pulmonary embolism now being considered, who were treated with dicumarol, there was no subsequent fatal pulmonary embolism or venous thrombosis; one patient had another non-fatal pulmonary embolism when the prothrombin value was between 20 and 30 per cent.

Incidence of Bleeding in 288 Medical Cases.—Two patients bled from the gastrointestinal tract and one had severe subcutaneous bleeding. Treatment was discontinued in all instances. All patients recovered. Minor bleeding (epistaxis, hematuria and petechiae) occurred twice. Treatment was continued in all instances. The incidence of bleeding (1.0 per cent for major bleeding and 0.66 per cent for minor bleeding) was markedly less than the incidence noted in the postoperative cases considered earlier in this presentation.

Conclusions from Experience with Medical Patients. Our experiences

indicate clearly that the anticoagulants are effective in the treatment and prevention of vascular thrombosis of medical patients just as they are effective in the care of postoperative patients with these conditions. Fatal pulmonary embolism can be prevented and venous and arterial thrombosis can be halted in most instances.

Summary of Experience with Anticoagulants. 1) The expert use of the anticoagulants, heparin and dicumarol, has improved tremendously the outlook for patients who have acute vascular thrombosis.

2) An over-all consideration of 1,513 postoperative patients treated with anticoagulants indicated that the following results were achieved: 85 patients survived who would have been expected to die from pulmonary embolism; 250 patients were spared venous thrombosis or non-fatal pulmonary embolism. In 506 additional postoperative cases in which dicumarol was used prophylactically, venous thrombosis occurred in but two instances; there was no pulmonary embolism.

3) A consideration of 288 medical patients indicates that fatal pulmonary embolism was prevented by anticoagulants. Non-fatal pulmonary embolism and venous thrombosis occurred very infrequently.

4) In general, the use of anticoagulants constitutes the greatest contribution to the successful treatment and prevention of intravascular thrombosis and embolism.

The final questions relative to thrombophlebitis are two. How long does the physician continue anticoagulant therapy and what should he do once the acute phase is over? For the purpose of simplification I shall consider only thrombophlebitis of the deep veins. Ordinarily we continue anticoagulant therapy for about 10 days unless there is evidence of progressive venous thrombosis. I am uncertain about ambulation in the presence of acute thrombophlebitis of the deep veins. I know that some physicians advocate ambulation at once. There is danger certainly in keeping patients in bed over a long period of time. On a number of occasions I have had patients, who according to their statements have been kept in bed several months because, as the physician has said, to become active at an earlier period, might endanger the patient's life from pulmonary embolism. This program usually leads to an acute anxiety state, a profound psychoneurosis. Whatever the physician may believe about the possibility of pulmonary embolism, he should never transmit his belief to the patient although it may be wise to discuss the situation with relatives. I believe a median course is advisable as far as

activity is concerned. Usually I recommend ambulation when edema has largely or wholly disappeared.

The final consideration in deep thrombophlebitis is the management when the patient becomes active. This can be stated in two words. Prevent edema! This is accomplished by adequate bandaging. The test of adequacy is whether or not edema occurs when the bandage is worn. Ordinarily, the cloth-elastic bandage known as Ace bandage or tensor bandage is inadequate. The best bandage, by all means, is the pure gum rubber bandage 3 inches wide and 15 feet long. No attempt is made to bandage above the knee. The edema there disappears in time. The bandage is applied in the morning usually over a lisle stocking. If there is much perspiration it is well to change the stocking and re-apply the bandage at noon. Naturally it is not worn at night. I know little advantage to instructing the patient to sit with the leg on a stool or chair or to elevating it while he is in bed. Once every month the patient discards the bandage for one day. If edema occurs the bandage is worn for another month. Many patients can discard the bandage forever within three to six months.

Bandaging after acute deep venous thrombosis is sadly neglected and accounts for the large number of patients who eventually develop varices, stasis dermatitis, and stasis ulceration. It appears unquestionably true that these complications seldom or never occur when the program of bandaging is carried out.

In this presentation I have attempted to present the highlights of acute thrombophlebitis. A good deal of material has been omitted. Also I have repeatedly expressed opinion rather than proved facts. I have done so only because facts are rare in medicine and because my opinions are based on considerable experience with thrombophlebitis.

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SOME PRELIMINARY OBSERVATIONS ON THE CLINICAL COURSE OF MYASTHENIA GRAVIS BEFORE AND AFTER THYMECTOMY*

A. M. HARVEY

Professor of Medicine, Johns Hopkins University School of Medicine

THE disease myasthenia gravis has attracted the attention of clinical investigators for many years because of its numerous physiological implications. The earliest clinical description of this disease was made by Willis in 1685.[1] In speaking of the various types of palsy he stated: "There is another kind of this disease depending on the scarcity of the spirits in which the motion fails wholly in no part or member yet is performed but weakly only or deprivedly by any. Those who being troubled with the scarcity of spirits, will force them as much as they may to local motions, are able at first rising in the morning to walk, move their arms this way and that or to lift up a weight with strength, but before noon the stores of the spirits which influence the muscle being spent they are scarce able to move hand or foot. I have now a prudent and honest woman in cure who for many years has been obnoxious to this kind of bastard palsy, not only in the limbs but likewise in the tongue. This person for sometime speaks freely and readily enough but after long, hasty or laborious speaking presently she becomes mute as a fish and cannot bring forth a word. Nay, and does not recover the use of her voice until after many minutes."

There are now available accurate methods of measuring neuromuscular function. Many drugs have been found which produce rapid changes in muscle function in these patients, and one is able to make quantitative chemical studies of an enzyme system which has a relation to neuromuscular function. However, there is still very little more of an understanding of the pathogenesis of this disease than when Willis wrote at the conclusion of his description: "The spirits residing in the

* The Department of Medicine and The Medical Clinic of the Johns Hopkins Medical School and Hospital, Baltimore.
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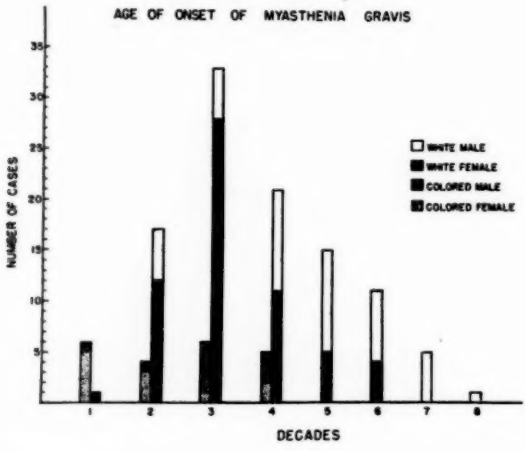
CHART I



brain are conscious of the weakness of the others placed in the members. They refuse to impose local motion on their companions as being a task too difficult for them, for which cause the affected are scarce led by any persuasion."

Myasthenia gravis was thought to be a rare disease until recent advances in diagnosis and treatment became available. These have led to the recognition of an increasing number of cases making possible an evaluation of the natural history of the disease and the situations and circumstances in which it develops. It seems worth while now to review our knowledge of the clinical evolution of this disease for we may find it leads to an understanding of certain relationships between the normal function of the neuromuscular system and of the thymus, relationships which may not emerge from an intense physiological study of an individual case. It is my purpose this evening to describe to you some impressions from the preliminary analysis of 125 cases of myasthenia gravis. Interest has been focussed on the pattern of development of this disease before and after the institution of neostigmine therapy. The results of thymectomy will be reviewed against this background.

The thymus has long been an organ of mystery. Its relationship to myasthenia gravis seems more than coincidental. The results of total

extirpation of the thymus in this abnormality have been variable. Without a more thorough knowledge of the natural course of the disease they cannot be properly evaluated. An understanding of factors responsible for the variable effects of thymectomy may be difficult to obtain. It might transpire that when striking improvement occurred it was merely a spontaneous change and not directly related to removal of the thymus. On the other hand, it is quite possible that such remissions do represent direct effects of the operation. Further, it is possible that failures to improve following operation may have occurred because the disease had reached a stage in its development which precluded a lasting return of muscle power or that a similar situation had been created by the preoperative treatment. It should also be pointed out that because thymic tissue may be widely scattered complete extirpation may be a very difficult surgical maneuver.

The incidence of this disease with reference to sex and race in relation to age at onset provides some points of interest (*Chart 1*). Of the total of 125 cases 57 per cent were in females, 43 per cent in males; 20 cases or approximately 16 per cent were in Negroes. The disease may begin in any decade of life. The youngest patient in this series was three and the oldest seventy-five years. The distribution by decades was 7 cases in the first, 20 in the second, 39 in the third, 25 in the fourth, 15 in the fifth, 10 in the sixth, 5 in the seventh and 1 in the eighth. It is of some interest that 87 per cent of the female cases began before the age of forty. There was a peak in the incidence among females in the third decade. Following that there was a gradual falling off in the number of cases, none having its onset after the age of fifty-three. There was a more uniform distribution of the cases occurring in males, 56 per cent having their onset below the age of forty, 44 per cent beginning after this age in contrast to only 13 per cent of the cases in females. When one analyzes the cases occurring in the colored race a somewhat similar pattern emerges. In the early age groups there was a predominance in females. It is of considerable interest that none of the cases in Negroes had its onset after the age of thirty-four and that of the cases with onset before the age of ten, six out of seven were in Negroes, only one being of the male sex. It is quite obvious that this analysis must be tentative because of the unrepresentative sampling which may result when patients come from a wide area to a center interested in a particular disease. However, this analysis does confirm clinical

TABLE I

POSSIBLE PRECIPITATING FACTORS ASSOCIATED WITH THE ONSET OF MYASTHENIA GRAVIS

Acute Upper Respiratory Infection		16
Post-Operative Infection		4
Acute Diarrhea		2
Pyelitis, Acute		2
Tetanus Antitoxin		1
Hyperthyroidism		5
Pregnancy	During	1
	After Delivery	3
Menstruation		2
Emotional Strain, Severe		4
Electric Shock with Unconsciousness		1
Sun Stroke		1
Carbon Monoxide Poisoning		1
Strenuous Exercise		2

impressions gained over a period of years concerning certain sex and race patterns in relation to the age of onset of myasthenia. In the first decade the typical picture usually is seen in Negro females. In the second and third decades there is a striking predominance of cases in white females while cases in which the onset is late in life characteristically are white males.

It has long been recognized that acute infections, pregnancy, hyperthyroidism and severe emotional tension often precede the onset of this disease. A survey of this series of cases reveals the familiar distribution of these factors associated with the onset of the disease as shown in the accompanying table (Table I).

That sensory disturbances may precede or accompany the first manifestations of weakness is not generally realized. Headache, pain in the eye, numbness and tingling in various regions and other sensory manifestations were described often enough to deserve some consideration. The accompanying table (Table II) shows the incidence of these manifestations in this series of cases. It is worth pointing out that pain

TABLE II

SENSORY DISTURBANCES AT ONSET

Pain in Eye	5
Numbness and Tingling	
Arms	4
Face	3
Lips	2
Neck	1
Legs	1
Tongue	1
Generalized Paresthesias	2
"Cramps"—Arms and Legs	2

TABLE III

CASES WITH SUDDEN ONSET

Ptosis	10
Diplopia	9
Legs Gave Way	7
Weakness of Mastication	1
Nasal Speech	1
Dysphagia	1
Facial Weakness	1

in the eye led to the diagnosis of aneurysm in two cases resulting in the patients having angiograms and in one instance undergoing a ventriculogram.

Although the onset has been generally described as gradual in cases of this illness, it has been rather impressive in this series that in many instances the first manifestation appeared with such suddenness that the patient was able to date and time the onset very accurately. The accompanying table (Table III) shows the initial symptom in the cases which began precipitately; in the majority of instances ptosis or diplopia appeared first, but it is important to emphasize that the extremities may be the location of the first functional alteration. It is in these cases with dramatic and sudden appearance of symptoms that the diagnosis was not recognized and some vascular abnormality was suspected. The following brief case summaries may serve to illustrate this feature of the disease:

A thirty year old white housewife had acute gastro-enteritis in May, 1939. Ten days later while driving her car she suddenly developed diplopia and drooping of the right lid. She was forced to stop the car on the side of the road and could not proceed until she discovered that double vision vanished when she closed one eye.

The second patient, a sixteen year old white girl, fell suddenly while playing volley ball and could not move her legs for a period of one-half hour. In climbing steps afterwards she noticed extreme weakness of her

TABLE IV

SUMMARY OF INITIAL SYMPTOMS IN MYASTHENIA GRAVIS

Ptosis	Unilateral	28
	Bilateral	15
Diplopia		35
Weakness of legs		18
Generalized Weakness		10
Weakness of Hands, Forearms		9
Dysarthria		12
Dysphagia		9
Difficulty in Mastication		7
Facial Weakness		4
Neck and Shoulder Weakness		2

legs. Several months passed before the next manifestation, ptosis, appeared.

Initial symptoms in this series of cases were similar to those which have been reported previously. The figures in the accompanying table (Table IV), however, show one feature which should be emphasized. This disease may have its first manifestation as weakness of a generalized nature or localized to the arms or legs. It is also worth pointing out that at the onset the involvement may be limited to a very small region. Paresis of one external rectus or the extensor of one finger may be the only recognizable involvement for a long period of time.

In the majority of instances ptosis and diplopia are the first evidence of difficulty. For this reason it seems important here to reëmphasize certain characteristic features of the involvement of the eye muscles in this disease. In recent years ophthalmologists have become aware of the unique features of myasthenia of the ocular muscles and many of our cases were first recognized by the eye specialist. Dr. Frank Walsh[2] has recently analyzed the ocular manifestations in this series of cases of myasthenia gravis and the following points seem worthy of emphasis:

1. Ocular signs or symptoms were present at some time in all cases.
2. Purely ocular myasthenia gravis was observed several times, but in such cases there is always the possibility of spread of the weakness at a later date.

3. Ocular symptoms and signs usually appear early in the course of the disease but occasionally they are a late development.
4. Ptosis is the most common sign.
5. Edema of the lids is a rare prodromal sign.
6. Retraction of the lids is a rare ocular sign which was observed in two cases after ptosis of long standing.
7. The abnormal associated movements of the lids in myasthenia gravis are similar to those resulting from misdirection of regenerated fibers in the third nerve.
8. Weakness of the orbicularis oculi may occur with or without ptosis. Weakness in closure of the lids is overlooked more often than any other common ocular sign.
9. Limitation of ocular movements occurs unilaterally and bilaterally and in almost all combinations.
10. When pupillary abnormalities are present it is doubtful that the case is one of myasthenia gravis.
11. Changes in accommodation were observed in only one case.
12. Visual fields and visual acuity were not altered.
13. The similarity of the ocular signs seen in myasthenia and in hyperthyroidism is worthy of note.

Once the disease has appeared the course may follow a number of patterns. There may be gradual extension of the involved areas leading to a relatively steady state of weakness which, once having reached a level, remains essentially unchanged over a period of years. In the second group there is rapid progress both in the extent of the involvement and its severity, sometimes terminating in death within a very few weeks. In still another type ocular symptoms may be the only evidence of myasthenia over a period of many years. The impression has been gained that patients in this group are predominantly in the later decades.

Since the general recognition of this disease as a separate entity, emphasis has been placed on the tendency for the symptoms to fluctuate in severity and for spontaneous remissions to occur. It is this tendency of the disease to vary in severity from time to time in any one patient that makes any deduction regarding the value of treatment a difficult and delicate matter. Because one of our aims is to evaluate a specific form of treatment in this disease attention will be devoted now to those cases of myasthenia gravis which present a clinical picture of remissions and exacerbations, of which the following is an example:

The patient was a 28 year old white female who entered the hospital in May, 1931, complaining that three weeks previously she had noted the sudden onset of double vision, which gradually increased in severity over a period of three days. Examination at that time revealed weakness of the internal rectus on the left with slight weakness of the facial muscles on the same side. There was moderate ptosis of the left lid. During the next few weeks in the hospital the ptosis and internal rectus palsy were intermittently present. On June 25, 1931 it was noted for the first time that both strabismus and ptosis had vanished. On September 1, 1931 the patient returned to the hospital stating that her previous symptoms had returned and also complaining of fatigue on speaking and swallowing. During the next four years this basic constellation of symptoms was always present. In addition, her illness was characterized by recurrent attacks of generalized weakness with inability to speak or swallow. Often she would choke over her food and at times could not hold objects in her hand. These attacks occurred four to five times a month, lasted for several days at a time, and seemed to be precipitated by exertion. In October, 1935, she contracted an upper respiratory tract infection, her general weakness suddenly became very marked and she could swallow only small amounts of liquids. She could not phonate and had to communicate by writing. On the following day she could take nothing by mouth and began to gasp for breath. At that time she was found to have a temperature of 102°F with evidences of bilateral lobular pneumonia. She was obviously very acutely ill and in marked respiratory distress. There was bilateral ptosis, more marked on the left. Her facial muscles were quite weak and the pharyngeal and palatal movements were absent. She had complete aphonia. There was marked generalized weakness which became rapidly worse with even slight movement. Neostigmine had only been recently introduced at that time. She was given what now would be considered inadequate dosage. There was striking temporary relief, but the effects decreased with subsequent injections and the patient died in spite of artificial respiration.

This sequence of events is fairly representative. The patient had a complete remission lasting for a few months early in the course of her disease. A relapse occurred with involvement of the eyes and pharyngeal muscles. This level of weakness never disappeared after this relapse and the course of the disease was punctuated during the final four years by frequent periods of marked exacerbation of symptoms lasting for a few

days at a time with precipitation of a fatal myasthenic crisis by a respiratory infection.

Kennedy and Moersch in 1937[3] published a clinical review of eighty-seven cases of myasthenia gravis and analyzed the remission pattern. They used the term complete remission to describe seemingly total recovery lasting for more than one month and permitting patients to resume their former occupations. A partial remission indicated some improvement lasting for months or years. They did not classify moderate fluctuations of symptoms as a clinical remission. Twenty-seven patients had a total of forty-three complete remissions which ranged from one month to sixteen years. The average duration was 2.2 years, but the majority lasted less than one year. They state that it is quite probable that some of their so-called complete remissions should have been classified as only partial. They found that thirteen patients had seventeen partial remissions which lasted from less than one month to sixteen years, the average duration being 1.5 years, but the majority enduring for less than six months. The duration of the illness in thirty-four patients known to have died varied from six months to twenty-two years, with an average duration of 4.5 years.

Since these cases were all studied prior to the introduction of neostigmine therapy, it is of interest to see what the remission pattern has been in the present series of patients. Essentially the same criteria have been used to define a clinically significant remission. In this series of cases thirty patients have had a remission, twenty-two prior to the administration of any neostigmine and eight during neostigmine therapy. It is of interest to analyze the remissions in patients who were receiving neostigmine therapy. These eight patients had received neostigmine for an average of eight months with a maximum time of thirty-six months and a minimum time of two months. In two of the patients the remission occurred during the few weeks following x-ray therapy to the anterior mediastinum, including the patient who had been on treatment for thirty-six months. If one excludes these two patients, the remaining six had received this drug for a period of five months with a maximum figure of twelve months and a minimum of two.

As a base line for comparison with patients who have undergone thymectomy and will be discussed later, the following figures are of interest. Eight patients had a significant remission lasting from three months to two years. These remissions appeared on an average three

TABLE V

REMISSIONS IN MYASTHENIA GRAVIS
2 YEARS OR OVER

Duration of Remission	*Degree*	*Mo. After Onset Disease*	*Mo. After Neostigmine*	*Assoc. Factors*
15 yrs.	+++	3	——	——
5 yrs.	+++	24	5	——
5 yrs.	++	1	——	——
4 yrs.	++	24	——	——
5 yrs.	++++	¾	——	——
4 yrs.	++++	2	——	——
3 yrs.	++++	36	——	——
3 yrs.	+++	1	——	Relapse with pregnancy
3 yrs.	++	1	——	——
2 yrs.	++++	1	——	——

TABLE VI

REMISSIONS IN MYASTHENIA GRAVIS
6 MONTHS TO 2 YEARS

Duration of Remission	*Degree*	*Mo. After Onset Disease*	*Mo. After Neostigmine*	*Assoc. Factors*
18 mo.	++++	2	2	Symptoms disappeared after pregnancy
14 mo.	+++	3	——	——
12 mo.	+++	3	2	X-ray Thymus
8 mo.	++++	3	3	Neostigmine dosage progressively decreased over 3 months
6 mo.	+++	36	36	X-ray Thymus
4 mo.	+++	5	3	——
4 mo.	+++	½	——	——
3 mo.	+++	6	3	Onset followed pregnancy

months after the initial symptom of myasthenia. The longest period being six months and the shortest period two weeks. In nine patients there was a remission lasting from two to fifteen years. In this group the average time after onset of the initial symptom to the development of the remission was eight months. The longest period being thirty-six months and the shortest period three weeks.

The accompanying tables (Tables V and VI) show a more detailed picture of the remission pattern in this group of patients. It will be noted that only one patient had a remission lasting for two years or over after the onset of neostigmine therapy. In this instance the patient was a fifty-five year old male who had predominantly ocular myasthenia. In the group in which symptoms abated for from six months to two years many of the patients had been on neostigmine therapy. All, however, had taken this drug for three months or less with the exception of one case in which the remission developed following x-ray therapy to the thymus. It is of interest that sixty of the 125 patients gave a definite history of having had no significant remissions during the course of their myasthenia.

It is recognized that these data are not sufficiently extensive from which to draw any definite conclusions. However, they do point to certain possible variations in the course of myasthenia before and after the institution of neostigmine therapy. In the early stage of the disease remissions may occur for periods up to at least fifteen years. As the duration of the disease lengthens the probability of a lasting remission of clinical significance grows less. It is also evident that only occasionally does the disease regress once neostigmine therapy has been introduced. The limits of variation, however, are wide, making a definitive evaluation of a procedure like thymectomy extremely difficult. However, the majority of the patients in this series of 125 cases received neostigmine therapy at a fairly early stage in their myasthenia gravis, and it may be of some significance that the most striking remissions and those of longest duration occurred in the relatively small number of patients who had never received any drug treatment.

There is much material of interest in this series of cases regarding factors which influence the intensity of symptoms during the course of this disease. Upper respiratory tract infections almost uniformly result in an exacerbation lasting for a variable period of time. Usually the disease returns to the pre-infection level of severity within a few

days, but occasionally an infection acts as a precipitating factor producing a lasting increase in severity. The onset of the myasthenia in several instances has taken place in a setting of hyperthyroidism, and in at least two cases there has been a very significant reduction in symptoms of myasthenia following thyroidectomy. Pregnancy also influences the course of this disease but the pattern is not always consistent. It has been uniformly true that the disease became more severe following the birth of the child. Menstruation has a very characteristic relationship to the level of symptoms in myasthenia. Almost all female patients will notice an increase in the severity of their weakness for several days before the onset of menstrual flow. After flow begins, either immediately or within a period of a few days there is an abrupt improvement and the female myasthenic feels at her best immediately after the menstrual period. It might be of interest to site an example in which the disease had its clinical onset in relation to the menstrual cycle:

The patient was a forty-two year old white female who became aware in March, 1942 of a peculiar sensation in the facial muscles which she described variously as numbness and twitching. Just before her next menstrual period she noted a generalized feeling of weakness. Following this her menstrual periods became irregular. In October, 1942 just before onset of menstruation the patient developed diplopia and bilateral ptosis. These symptoms disappeared after the menstrual period was over. In January, 1943 again just before menstruation, the patient became aware of difficulty in chewing and was restricted to a liquid diet. This time the symptoms improved after the onset of flow but did not completely disappear. One month later, again just before onset of her period, her speech became involved and she developed generalized weakness.

The influence of infection and menstruation is emphasized as their consistent effect on the course of myasthenic weakness may be of value in estimating the degree of the myasthenic state after thymectomy.

The frequency with which adenoma and hyperplasia of the thymus are encountered in patients with myasthenia has emphasized the possible role played by this organ in the pathogenesis of the disease. In at least one instance prior to 1941 a thymic tumor had been removed following which there was distinct amelioration of the patient's symptoms. It was believed that in order to evaluate the possible relationship of the thymus to the pathogenesis of myasthenia, total extirpation of all thymic tissue should be undertaken in a series of cases. This was begun in 1941 in

TABLE VII

RESULTS OF THYMECTOMY

Group		(1)	(2)	(3)	(4)	(5)
Age (Aver.)		32	29	26	26	38
Sex	M	2	1	1	2	4
	F	0	5	6	3	2
Mo. Pre-Operative Treatment with Neostigmine		1	11	29	21	19
Type of Thymic Change	Hyperplasia	1	5	6	5	2
	Thymoma	1	1	1	0	4
Pre-Operative Remission (Aver.)		0	One with pregnancy	One partial for 3 yrs. pre-neostigmine	One with preg. pre-neostigmine One for 4 mos. pre-neostigmine	0
Mo. with Myasthenia Pre-Operative (Aver.)		17	28	40	47	22
Mo. Post-Operative Follow-Up		79, 34	67, 62, 36, 36, 27, 21	78, 70, 48, 9, 6, 6, 6	63, 54, 22, 13, 6	37, 26, 12, 6, 6, 5

GROUP (1) = Well
GROUP (2) = Almost well
GROUP (3) = Moderate Return Toward Normal Strength
GROUP (4) = Slight but Continued Improvement
GROUP (5) = Unchanged

collaboration with Alfred Blalock, J. L. Lilienthal, Jr. and F. R. Ford[4, 5] and since that time thirty-two patients have had their thymus removed. In seven of these a circumscribed tumor was found and in the remaining twenty-five variable amounts of hyperplastic thymic tissue. Three of the patients died in the immediate post-operative period and seven others have died subsequently. All of these patients had a severe form of the disease. Twenty-six have been followed for a period of at least six months since operation. Two patients are well, six have shown an almost complete remission of symptoms, seven have had a partial return of their strength toward normal, five have shown definite but slight and continued improvement and in nine the course of the disease has not changed. The accompanying table (Table VII) shows a more detailed analysis of the results. There are several points of interest. It is well rec-

ognized that the number of cases is too small for reliable analysis, but certain trends are evident which may be of some importance in evaluating the results. In the first two groups which have shown a highly significant degree of remission or complete loss of symptoms pre-operative treatment had been administered for a much shorter period of time than in the groups showing only slight or no remission. The difference in the duration of the disease itself before thymectomy was not striking in the various groups. It is also noteworthy that few of these patients had had any tendency to spontaneous remission in the pre-operative period. It is well to reëmphasize that these patients had a severe form of the disease and most of them were taking large amounts of neostigmine at the time of operation. We have already noted the infrequent appearance of remissions after a patient has been taking this drug for any considerable period of time. Many of the patients were not able to forego neostigmine after operation and this may have lessened the possibility of a post-operative remission. It also may account for the relatively slow time course of the improvement following operation in many of the patients. Of those patients in the first two groups, four now give a definite history that colds no longer influence their muscular strength, and in two of the female patients the characteristic alteration in strength related to the menstrual period has disappeared. In the patients showing little or no improvement, four have shown no change in regard to the influence of infection of the upper respiratory tract on the course of their disease, while six still note the characteristic change in relation to the menstrual period.

In large degree the estimations of improvement have been based on objective changes rather than the alteration in the amount of neostigmine therapy which the patient required. The state of the patient on awakening in the morning, having received no neostigmine during the night, has provided a useful criterion for estimating post-operative improvement. Also some emphasis has been placed on various physical acts which the patient was able to do after operation but not before, with consideration given to the amount of neostigmine being taken in each period.

A summary of the pre- and post-operative neostigmine requirements shows the following facts, the significance of which may be questioned because the attitude of the patient plays a large role in determining the amount which they administer to themselves. In the two patients who

TABLE VIII

DEATHS AFTER THYMECTOMY

No.	*Time Mo.*	*Thymoma*	*Thymus Autopsy*	*Post-Operative Improvement*	*Cause of Death*
1	12	+	0	0	Myasthenic Crisis
2	36	+	aberrant nodule neck	+++ (36)	Myasthenic Crisis during dysentery
			++		Sudden relapse
3	5	+	0	0	Myasthenic Crisis
4	6	+	—	+	Myasthenic Crisis
5	6	0	—	0	Myasthenic Crisis
6	40	0	++	++ (12)	Myasthenic Crisis
7	16	0	+	+ (12)	Myasthenic Crisis

Time is in months after operation to death.
In cases 6 and 7 partial improvement lasted for one year. In case 2 for 3 years.

are well, one never had treatment prior to the operation, although his myasthenia was extremely severe, while the other was taking 24 tablets (360 mgm.) in the fourteen hour period when awake. Some years after operation the latter still requires no neostigmine. In the next group with very great improvement the average daily intake pre-operatively was 19 tablets (285 mgm.) and after operation 1.5 tablets (22.5 mgm.). In the next group with only moderate change the intake was 12 tablets (180 mgm.) before and 7 (105 mgm.) after operation, while in the last group with only very slight and questionable change the figures were 11 tablets (165 mgm.) before and 8 (120 mgm.) after thymectomy.

It has been postulated that the thymus gland is the source of a circulating curariform substance which produces the muscular weakness occurring in these patients. Support for this hypothesis was afforded by the clinical observation that in patients with thymoma the disease ran a fairly rapid course with progressive increase in severity. One would expect that in those individuals in whom a distinct thymus tumor was found at operation clinical improvement would be most dramatic. If one charts the deaths which have occurred in patients since thymectomy it is found, as seen in the accompanying table (Table VIII), that most

of them have been, excluding those which occurred in the immediate post-operative period, in those patients from whom a thymoma was removed. It may be noted that with one exception those patients failed to show any real improvement at any time in the post-operative period. One patient operated on within a short time after the onset of the disease and with little treatment before operation had a very satisfactory remission lasting for almost three years. Then, following an infection, she developed an acute exacerbation of myasthenia resulting in death, and at autopsy a nodule of aberrant thymus tissue was found in the neck. In view of the fact that three of the patients from whom a thymoma has been removed have died within the period of one year with no remission one might raise the question as to whether it is advisable to operate when a tumor is demonstrated. In support of this possibility is the following, rather unique, case: The patient, a white female housewife, noted at the age of 39 sudden onset of difficulty in opening the left eye. A few weeks later difficulty in swallowing appeared and on occasions fluids were regurgitated through the nose. The patient could not smile properly and had difficulty in talking. All symptoms were worse late in the day. Examination three months after onset of symptoms showed ptosis of the left lid, a very nasal quality to the voice so that speech was unintelligible and poor movement of the soft palate with essentially normal strength in the extremities. X-rays at that time revealed an abnormal shadow in the region of the aortic arch. The patient was placed on 30 mgm. of neostigmine twice daily and discharged. Two months later she was readmitted following an upper respiratory tract infection during which all of her symptoms had become exaggerated and she was taking 1 tablet of neostigmine every 2 hours. She recovered in a few days and was discharged taking 30 mgm. three times daily. She has been followed up to the present, has shown very little tendency for her disease to progress and rarely takes more than 115 mgm. neostigmine daily. The last x-ray taken on April 14, 1947, nine years after the first detection of a thymic tumor, shows a large mediastinal mass extending from the level of the first rib anteriorly downward to the point where it is hidden by the cardiac shadow. On lateral view the mass is seen to be in the anterior mediastinum superior and anterior to the heart shadow. This patient has had known myasthenia and a probable thymic tumor for nine years with no definite indication of progression of the disease and now is leading a reasonably normal life with the

aid of neostigmine therapy. However, it must be pointed out that of twelve thymic tumors seen in patients with myasthenia gravis in this series of cases three have been malignant with metastases present at the first examination. There is as yet no final answer to the question of whether or not the thymus releases a curariform substance. The weight of the evidence seems against the possibility.

One further comment seems indicated in regard to the post-mortem findings in the patients who have died after thymectomy. In three definite amounts of hyperplastic thymic tissue were found at autopsy. In all three there was a period of remission following operation and then relapse of the disease in the period before death. Only two of the other patients were examined by autopsy and in neither was any thymic tissue discovered. The significance of these observations is difficult to evaluate.

Summary

This preliminary analysis of 125 patients with myasthenia gravis suggests that if significant clinical remissions appear they tend to occur early in the course of the disease. Significant remissions which last for a long period of time appear to be unusual in patients who have received moderate or large amounts of neostigmine for more than six months.

Sufficient data are not yet available to evaluate with finality the effect of thymectomy on the course of myasthenia gravis. Preliminary studies indicate that the beneficial results are greater than one might expect from spontaneous remission in the severity of the myasthenia gravis. This conclusion is further supported by the following: that most of the cases operated upon had very severe myasthenia which had been present for more than six months, that there had been no tendency for the development of remissions pre-operatively, and that large doses of neostigmine had been administered in the pre-operative period and had to be continued for many weeks after operation.

If one may assume that the thymus does play a role in the pathogenesis of myasthenia gravis, the mechanism by which it does so is unknown. Much of present knowledge fails to support the suspicion of the elaboration of a curariform substance by this gland. As a possible clue to the normal function of the thymus an understanding of its role in this disease is important. Long term study of the effect of thymectomy early in the course of myasthenia gravis before prolonged therapy

with neostigimine may reveal information of importance concerning the physiological function of the thymus. The magnitude of this type of clinical experiment is evident when one realizes that spontaneous remission may occasionally last for at least fifteen years.

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THE INFLUENCE OF DISEASE ON HISTORY*

GEORGE T. PACK and FRANCES R. GRANT

MAN's history is a continuous struggle against oblivion. With each succeeding generation he renews the battle, fretted by the inherent urge to dominate his environment and perpetuate himself. In this timeless struggle, man's no less timeless enemies have been war and disease, and of the two, disease is the more insidious, since the weapons against it are the more elusive and imponderable.

So impotent at times has man found himself before this major antagonist, that for long ages he conceived disease as the instrument of a chastising deity. And to appease this Daemonic force, he invoked an entire pantheon of superhuman aids—bodhisatvas, saints and medicine men—to advocate his cause before the supreme rulers. Modern medicine no longer attributes the incursions of disease to the caprices of a too-human deity; it looks closer to man's way of life, to the environment in which he lives, to the human complex, which yields its secrets so reluctantly to the investigator.

This new rationale of disease, however, has not lessened the student's wonder at the extraordinary role of illness in shaping human history. As a protagonist in the drama of man, disease has played hero and villain; effected comedy and tragedy. A tyrant is stricken; a liberator enfeebled; an army contaminated; a people infected—and the denouement is changed!

In a brief sketch such as this, it would be impossible to do justice to the record. It is as long and complex as history itself. In a manner of speaking, it is longer than history itself. For, when the curtain of history rises, earth is already old and its hoary surface is dotted with the traces of man's progenitors. The medical investigator—the paleopathologist—allying himself with the archeologist and the ethnologist, scrutinizes each prehistoric fragment; the relic of Neanderthal man; the mummy of a Pharaoh; the trephaned skull of pre-Colombian man.

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From such as these, he learns that no Elysian immunity protected prehistoric man or beast. Even in that morning twilight, disease was man's ravager, although we may never know its complete role in the disappearance of those peoples that antedated our history.

With the inception of recorded history, man's destiny and disease are so interwoven that it is almost difficult to separate the threads. We are able only to scan some of the highlights, speculating casually upon their implications. Most obvious, of course, in this long record of disease and its influence on human history, are the great scourges that decimated entire peoples, rendering them a prey to their enemies, annihilating them in the slow agony of degeneration.

Until recently, the historian—reluctant to remove man from his role as the wilful master of his fate—failed to give disease its due, in the great historical changes. But it is difficult for the dispassionate student to ignore the ominous presence of pestilence as the threshold of almost every epochal transition. Like an entrepreneur, its macabre devices usher out the old cycle to make way for the new.

It is estimated that in the first seventeen centuries of our Christian era, plague appeared with fatal intermittency on the average of every four and a half years. And while the brevity of this sketch prevents us from venturing too greatly into the annals of pre-Christian history, we know that disease was then, no less a constant peril to life. One has only to study the Rig-Vedas, the Zend-Avesta, the Books of Confucius or the Buddhist Sutras, to realize that the threat of disease brooded over all man's ancient days. In our own Scriptures, plague and disease provide the accompanying organ-note and while the historian and physician may disagree with scriptural utterances as to the causes of the great Egyptian scourges, we know that by the Thirteenth Century B.C. plague had so debilitated Egypt as to permit the Jews to escape from their vassalage.

So, too, in Greece's history. With all truth, we may say that Plague, even more than any alien arms, proved the undoing of Athens. Never partisan in its attentions, disease appeared in Athens at the very time when Sparta was threatening its gates. Learning of the presence within Athens of this adversary, more terrifying than Athenian arms, the Spartan forces turned back. But within Athens, the plague continued its work—the long dissolution of Greece set in. The military was so decimated that the attempts to attack Sparta were lost before they were

begun. Pericles—that light of Greece—himself became a victim of the plague and with his death the Glory that was Greece had past, and the Gotterdaemmerung of Parnassus had set in. But the gods of Parnassus had succumbed not to man, but to an ignoble enemy; the rodents of Asia.

There is an awesome variant of the story six centuries later in Rome. Sparta had come and gone. The passion of Nazareth has passed almost unnoticed. Rome has reached its ultimate magnificence in the Antonines, a period called by Gibbons, "the happiest in the history of mankind." A happiness, alas, how fleeting! For at the very beginning of the reign of noble Marcus Aurelius, rebellion begins to stir in the Syrian city of Saleucia. The armies, dispatched from Rome to quell the uprising, return, not only with the laurels of victory, but with the seed of Rome's eventual destruction—the plague. For fifteen years it ravaged Rome. When it had finally spent itself, Marcus Aurelius himself had died, believed its victim. And with his death the Roman panoply fell apart. From his Meditations we may well take the moral of our story: "Observe how ephemeral and worthless human things are and what yesterday was a little mucus, tomorrow will be a mummy or ashes. . . . Nature which governs the whole will soon change all things which thou seest and out of their substance will make other things and again other things from the substance of them, in order that the world may be ever new."

* * * * *

It would be difficult to set down, in all its intricate detail, the chronology of pestilence in the succeeding Centuries, and its effect on mediaeval history. It struck, with ominous fatality, at times one country, at times another—pagans, Christians; kings, beggars; masters and serfs succumbed to its assaults. In the Fifth Century it stayed the advance of the Hun; in the Sixth it attacked Byzantium, sparing only the Arabs, who were thus able in the name of Allah to penetrate the European stage. It aided the Lombards against Italy and, in the Tenth Century, frustrated the armies of Otto. In the Eleventh, it decimated the German army in Rome, and in the Twelfth defeated the soldiers of Barbarossa. Time after time, it frustrated the efforts of the Crusaders, killing St. Louis himself, and allotting to Christendom, instead of the Holy Sepulchre, the thorny crown of disease and infection.

These are but a very few of Plague's ravages, which time and again transform Europe of the Middle Ages into a charnel house. But, in the light of subsequent history, they appear as steps to a horrendous finale; the planetary conflagration which was the Black Death.

It is doubtful if in all recorded history any force has so changed the course of human destiny as did this pestilence that scourged the world. Over the course of four centuries, it moved relentlessly over the face of the earth, consuming one people after another; decimating cities; depopulating nations; devastating continents. Not even the present war, which alone approaches in its world scope the Black Plague, will have affected so profoundly the course of human existence. When the Black Plague had spent itself, nothing in man's life remained quite the same. As Belloc said, "it was the one approach to a break in the continuity of human history."

Like many of the great plagues, it rose in the East—chroniclers tell us, it began in China, "following a great mist and stench". Thence, along the trade-routes, it passed to India, Persia and Russia, and Emperor John Catacuzene tells us of its presence in Constantinople by 1347. In October of that same year, it appeared in Europe at Messina, where, according to the Franciscan Friar, Michael of Piazza, and others, twelve Genoese galleys had taken refuge from a pursuing enemy. "These Genoese," says our Friar, "bore in their bones so virulent a disease, that anyone who but spoke to them was seized by a fatal illness and in no manner could escape death."

For the next four hundred years, writers in every corner of Europe were setting down additional macabre chapters of the story, tracing the plague's unarrestable advance from Malta, Cyprus, Greece, Sicily, Naples—on to France, Italy and Spain; then moving to Britain, Germany and Russia. Having saturated with infection all the known world, it became endemic in the countries it had ravaged, and flared up again and again until its final European outburst from 1663-68. Thenceforth, it trailed off into Russia, continuing to reappear there for the next hundred years.

The casualties of all wars are dwarfed by the mortality figures of this Plague—estimates of its victims range from Pope Clement's figure of almost forty-nine million to Hecker's estimate of twenty-five million. Suffice it to say, that the web of Europe's population remained completely threadbare—some 200,000 market towns had been wiped out,

in its course. Avignon reported a loss of two-thirds of its people; Venice, of 100,000; Bocaccio declared that Florence lost 100,000 of her 130,000 souls. England's clergy alone were depleted by 25,000. These are but a few of the devastating statistics of the Plague.

The effect on history of such a depletion of human forces is almost difficult of imagining. By wiping out great segments of population it shifted the trends of human activity. For instance, by annihilating a large portion of the mediaeval clergy, those guardians of Middle Age Scholasticism, it left the Church to heirs unprepared to cope with the spiritual unrest of Modern Man as he emerged from his mediaeval sick-bed. Thus was the Reformation precipitated.

By decimating the ranks of feudal lords and serfs it destroyed the manorial system. By thinning out the supply of workers, it tripled the wages of the available supply, and gave impulse to restrictive legislation and class struggles.

It unloosed swarms of lawyers who grew opulent in arguing the cases of succession and inheritance. It bred charlatans and rogues eager to profit by the chaos. It drove agricultural workers into the crowded urban centers and hastened the Industrial Revolution. It set men moving and migrating—within Europe to depopulated cities, whose rulers held out special enticements to immigrants, even be these thieves or criminals. It set men moving away from a Europe infested—bringing the cycle of discovery and colonization to its height, even as Europe's long Dance of Death continued.

It aroused strange libidos which translated themselves into cults such as the flagellants, the chorisants, the Children's Crusades, and a hundred others. All of Europe became a vast Witch's Sabbath, like some fantastic canvas of Hieronymus Bosch. To sum up, the Black Death turned the known world into a seething cauldron out of whose final residue emerged Modern Man.

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During the lengthy play of this major holocaust, other diseases were bursting out in lesser violence in various parts of the world, each pressing its own victory. Malaria, smallpox, typhus, leprosy, scurvy, syphilis, dysentery, and many others; each presents a saga in human misery with its subsequent influence on human history. Scurvy, for instance time and again delayed and re-charted the course of discovery,

looming as a more dread terror to the early sea-farer than unfathomed seas and legendary monsters.

Malaria, which Osler termed the "greatest destroyer of the human race," seeped the strength of nations through the centuries, transforming vital peoples into weaklings. Typhus, lying in ambush for army after army, rendered military victories meaningless by wiping out victors after they had conquered their foes. Syphilis, said to be the gift of the Spanish Conquistadors to the Motherland, which verily avenged Atahualpa, the Inca, by consuming forever after the armies of all Europe. Yellow fever, that guarded the American tropics more zealously than Yankee doctrines; twice staying France from invading the Hemisphere, once at Haiti and again at Panama. There are many more diseases too numerous to recount.

It is strange indeed, that save for a rare few, historians should have overlooked the historic consequences of all these assaults on humanity. Such classic historians as Thucydides, Lucretius, Herodotus and Plutarch, who lived through their challenge; or a later classicist, such as Niebuhr, sensed their importance. It is less to the historian than the literati, the poet, the cleric, the satirist and the artist that we must look, in studying the long chronicle of disease as a *force majeure* in human history; on rarer occasions to the physician. Fortunately we are able to weave a continuous thread of this story, as we follow the majestic account of a Thucydides, through the chronicles of the Kilkenny Monk, Procopius, Petrarch, Manzoni, Erasmus, down to a Bocaccio, De Foe, a Pepys or a Webster. It is a record of humanity frustrated by an unintelligible force; for as Niebuhr says, "it is not superstitious or even pious to look upon great plagues as a conflict of the terrestrial forces with the development of mankind." Most illuminating it is to study man in this long chronicle; under the threat of danger, the fabric of human relations wears thin; families separate; moral and ethical codes become meaningless. At times, however, this tempering gives renewed strength to man's inner strivings.

As impressive a picture of this story comes to us through the labors of the painters. Titian, for instance, whose paintings of the hero-saints of the Plagues—Roch, Sebastian, Cosmos and Damian—take on the symbol of supplication, as he himself is stricken. Or a Dürer, whose brush dips in the bile of the sufferer, himself. An entire panorama of human agony is rendered through a Simone Martine, Rubens, Guido Reni,

Caracci and many others.

And what, we may ask, of the physician during these times? Betrayed by its proponents and despised by its antagonists, no profession was ever so buffeted about as medicine in these tidal waves of human ailment. A pitiful remnant of medical men remains faithful to their calling—for the rest, as Guy de Chauliac, physician to Pope Clement VI, writes, their record is a mortifying spectacle of the frailty of mankind. On occasion they rise to grandeur, like an Hippocrates, who expends his frail utmost to aid his contemporaries, confessing finally to the possibility of a divine instrumentality in the devastation which he cannot stay. On the other hand, a Galen, physician to Marcus Aurelius, flees Rome at the first danger, returning reluctantly two years later at the exhortation of the Emperor, then writing a history of the plague brazenly plagiarized from Thucydides.

In Genoa, the Senators search the city vainly for three doctors who have remained to aid their fellows—though the black record is eventually erased by such a physician as Marco Leon who voluntarily left the then safety of Perugia, to aid plague-stricken Genoa; or a Chalin di Vinario, who even as he exposes his own life, ironically extols the physicians "who are prudent enough to hold back." Even the great Sydenham succumbs to the urgings of his family and puts London and the Black Death behind him—while the less-heralded Heinricio Sayer fearlessly attends patients, poor and rich alike, until he himself succumbs.

It is a curious record. But more curious, in the light of present-day medicine, are some of the medical expedients to which the doctors of the day resorted; amulets, bags of arsenic worn near the heart; the chewing of wormwood steeped in lemon; moss from the skull of a man who has met violent death, etc. It is little wonder that a Margaret Paston writes to her husband, in 1414, "For Goddys sake, be war what medesuns ye take of any fisusyans in London. I shall never trust to them because of your fadr and myn onkyl whoys sowlys God assuyle." So low did the repute of the doctor fall in the opinion of his contemporaries that in St. Lo, in 1601, the physician Marquier was accused of magic because he healed more of the ailing than his colleagues.

Sensing the impotence of the physician. the people themselves sought other panaceas. They turned their hopes most often to the self-abnegating men and women who nursed them, when their closest had fled. It

is these half-legendary figures such as Roch, Gerhard Groot, Sebastian, Cosmos and Damian, Procopius and others, who emerge out of the Middle Ages, with the aureole of hero-saints, anointed by the abysmal misery of an age in which humanity was unevenly pitted against its ancient antagonist—disease.

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And now let us turn from the larger canvas to its detail. Here our pattern is far more intricate and also more controversial—for it will always remain a moot question as to how greatly the life or death of any individual, his frailty or health, can affect the course of history. Tolstoy, for instance, decried vigorously the suggestion that Napoleon's illness at Borodino had turned the tide of battle. For him—as for others who see history as an unarrestable tide, as Schelling's "continuous revelation of the Absolute accomplishing itself"—the individual fades into a limbo of obscurity. For those, however, for whom history is the cumulative labor of generation on generation, man placed in a role of destiny may be important indeed. As Benedetto Croce says, "Let him who cuts individuals out of history but pay close attention that either he has not cut them out at all, as he imagined, or he has cut out with them, history itself."

On this premise—and it must be the premise of this sketch—the indisposition of Napoleon at Borodino becomes significant. Even more, the fact that Napoleon by the time of Borodino was perhaps already doomed by the alleged gastric cancer which was ultimately to kill him at St. Helena. The spasms which, time and again, in these later years, prostrated him, might well have been the real ally of the British and the Holy Alliance; might well, as Voltaire put it, have announced that God was already bored with the Corsican.

Let us go further. As witnesses ourselves to an epoch darkened by evil genius, we may find it profitable to analyze the physical composite of the Napoleonic man, for there are certain analogies that emerge in a scrutiny of these Luciferian figures that dominated their lives. In contrast to their frenzy to conquer the world, we uncover strange timidities, sexual inhibitions and perversions; in short, endocrine imbalance. Napoleon, so passionately anxious for an heir, could father only the unhappy and sickly L'Aiglon. As Anatole France perceived him, he was a buffoon who set the world by the ears, because he was unable to enjoy his own

marital bed. Caesar, imposing his will on the world, philandered with equal promiscuity among men and women. Hitler, withal his frantic *Weltanschauung*, finally will probably only exude the miasma of the homosexual and megalomaniac.

Nor are lesser personages spurned by disease in its manipulation of history—it accompanies princes and royal scions in their marriages of convenience, carrying the mental and physical taints of the dynasties across the chess-board of Europe. Its effective servant—inbreeding—does the rest and accomplishes the pollution of Bourbons, Hohenzollerns, Hapsburghs and Romanoffs. How masterfully, for instance, with one stroke, it demolishes the Romanoffs and Spanish Bourbons, with marriage as the enticement. For what royal princes would not have relished an alliance with the granddaughters of the great Victoria! Yet to both Nicholas of Russia and Alfonso of Spain, their marriages brought the fatal Battenberg bridal gift. The heirs apparent to both houses inherited the hemophilia which is one of the taints of German royalty. Surely, to this fatal blood strain must be attributed the hastened revolutions of both Spain and Russia. And what an episode for the "Garden of Horrors" is this final Russian Grande Guignol of the Mad Monk, the terrorized Tsarina and the little Tsarevitch!

Deftly, also, has disease dissipated other dreams of Empire; Attila suddenly stricken; Alexander conquered by fever; Henry V of France; Charles V, almost attaining the dreamed-of European Empire, merely to be conquered by gout; witness the rapid disintegration of his vast inheritance under fanatical Philip II, with the melancholy strain of his mad grandmother working tumult within him. Gout may also have helped to rob Britain of her greatest colony, when it deprived George III of the counsel of Chatham, the one minister who was sympathetic to America and might have won over the king. Gout and its effect on the affairs of men might alone, in fact, well be the topic of a complete study, as Sydenham (himself a victim) points out.

What a field for study, also, are the numerous royal psychopaths—a veritably inexhaustible field in which the psychiatrist might collaborate with the pathologist and eugenicist. Take Frederick the Great, as a youth beauty-loving, charming, happy-go-lucky; goaded by his father into the brutal and relentless warrior. Impotent by twenty-three, he pursues a loveless life, as famous for his aversion to bathing as for military genius.

Or Henry VIII, who began life as a pleasant, not-too-hopeful second son and was precipitated by the death of his elder brother onto a throne, to become a lecherous, syphilitic and finally paretic king whose physical appetites sow the seeds of Britain's problems for generations. Brooks Adams, philosophizing on history, makes the comment that had Henry been "hampered with scruples, honour, truth or conscience, he too might have been undone". A comment that might well apply to many of Europe's royalty and for much the same reason.

And now, with special appreciation of its bitter fruits for our times, we might mention another historic episode—with Wilhelm Hohenzollern of the withered arm playing the chief role. This deformity (brachial palsy) was a birth-gift for which the late Kaiser never forgave his parents. And yet, pleasant enough parents they were—Frederick III married to the daughter of Victoria and growing ever more sympathetic with the democratic institutions of England. How unlike the ravenous entourage of their Prussian court! Mere weeks after his ascension to the throne, disease, like some apocalyptic rider, overtakes Frederick—in the form of cancer of the larynx. He is desperately anxious to stay alive—for no sovereign ever had fewer illusions about his heir, or the menace that his succession might mean to the peace of the world. From our present perspective, we see an ominous augury in the obscene eagerness with which Wilhelm awaits his father's death, even penning a pompous edict of accession, long before the physicians have even agreed on the fatal character of the disease. Here, alas, disease plays the villain's accomplice. Frederick dies, and, with his passing, generations of the world's youth are doomed to bloody martyrdom.

Or let us examine another episode—this time with the same disease making a graceful withdrawal. In June 1893, President Grover Cleveland discovers that he, too, is stricken with cancer of the superior maxilla. It comes at the most critical moment of his administration. Antagonisms are running high over the "free silver" issue; the President, an ardent opponent of the measure, is prepared to ask for a repeal of the "free silver" clause although his own vice-president is an advocate of the measure. A financial crisis will inevitably be precipitated even by a rumor of his illness. Therefore, at once and with complete secrecy, the President and his physicians arranged an operation on the Yacht Benedict, in Long Island Sound. In two successive operations much of the President's jaw was removed and an artificial or dental moulage

substituted. A month and a half later, Cleveland appeared before Congress, appealing for the repeal of the free silver clause–and won his plea. No one was aware of the crisis through which he had passed–nor is it mentioned in the fifteen subsequent years in which Cleveland lived, free from recurrence of the malignant tumor. Only after his death was the episode disclosed by one of the surgeons who had participated. Here disease is seen in a rarely amenable mood–for once moved, we may hope, by the dignity and merit of the victim, although modern medicine would rightly lay the victory to the quick diagnosis of the disease and the unhesitating attack upon it.

Less felicitous in their outcomes are the numerous sudden deaths which often have altered historical finales; Mirabeau, the one strong force which might have averted the blood baths of the French Revolution; Cavour, at the moment of Italy's great need of him; Baron von Bilbesten, whom Asquith believes should have averted the First World War–perhaps preventable deaths, which may have changed the narrative of history.

These are but a few of the episodes in the phantasmagoria of kings, warriors and statesmen, but they permit a rapid glance at the work of that unpredictable arch-strategist, disease.

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But then history is not alone a tale of kings and warriors. There is more permanent history created by scholars and artists. Here certainly, the historical credos of Schelling and Croce might well merge–for where, if not in the creations of man's mind and spirit, is the Absolute constantly accomplishing and reflecting itself? In this phase of our sketch, concerned with disease and its effect on history through genius, a pattern unfolds in which disease seems most often to work on the side of the angels. Nature, it would seem, as the most thrifty of husbandmen, will not waste a drop of the passion called genius, and uses even pain for its purposes.

As Sigerist points out, disease is an experience, and the artist (let us add also the scientist and philosopher), being the most sensitive of men, can hardly fail to be affected by it. Yet it is not alone in its psychic influence that disease affects genius. Even the pathologic and toxic incursions of disease seem to bear a direct relation to his creation and, very often, to the very type of his creation. We are beginning to dis-

cern, although we cannot always explain, this relationship—and critic, historian and physician should find an excellent field of common labor in studying the patterns together.

Like fire, which heats as it consumes, disease seems to release a creative glow in the wasting body of the creator. Even when it shortens life, as in the case of a Shubert, a Schiller, a Doctor Laennec, or a Mozart, it has so spurred the spirit in its race with death as to have gained the full bounty of creation, within the shortened span.

Tuberculosis, for instance, is so interwoven with man's creation, that it would be impossible to list the innumerable artists and scholars who labored with its consuming breath constantly upon them. And there is no mistaking the character of their work. Dr. John Brown of Edinburgh called tuberculosis "that sad malady in which the body and soul burn together—as in oxygen gas—as if knowing their time is short." A creative intoxication, always speedward, pervades their offerings; Watteau visioning a perpetual Arcady, which he might never enter; the nostalgic ecstasy of a Shelley, a Keats, a Katharine Mansfield, a Lanier, the doomed Brontës, Stevenson, and a host of others.

To see the tuberculous great in best relief, compare a Francis of Assisi, envisioning religion as an eternal ministry to beauty; and Loyola, lamed by his wound, narrowing his faith into a terrible scourge of self-discipline and vigilance. In the Assisian, that "morning star of the Renaissance," we see the epitome of the tuberculous genius, whose spiritual passion rises as the body wastes, leaping to death as it were, with a joyous "Hymn to the Sun." Sometimes, as in the case of an Emerson, a Goethe, a Kant and especially a Spinoza, the spiritual urging of the tuberculous genius becomes so profound as to inspire a universal message on a cosmic key. At other times, when surcease of pain is sought through opiates, as in the case of Poe, Coleridge, Rossetti or Francis Thomson, we can detect a new note in the creative expression, the "stigmata of the drug imagination" as it is termed by Jeanette Marks, who rightly points out that what is often the most beautiful in their works, is the most deranged. A similar distortion of the spiritual focus is alcohol's contribution to the work of a Dowson, a Beardsley, a Joyce or an Andreyev.

The apotheosis of the creative genius, sinking through illness and drugs, to produce its most lofty utterance, is seen in Francis Thomson, who writes "The Hound of Heaven" in the midst of his ultimate phy-

sical humiliation. In his awareness of this strange creative anomaly, he utters an outcry which might well serve as our own query; "Designer Infinite, must thou char the wood ere thou canst limn with it?"

Now let us turn to disease in the role of chastiser–here its rebuke is subtle enough to arouse the determination to compensative creation. Beethoven's deafness was of such character. As he himself wrote, "How am I to admit infirmity in the one sense which should have been more perfect in me than in others?" Yet out of the silence which shut out a strident world–or because of it–Beethoven found the flood of his extraordinary harmonies. Undoubtedly, Milton's blindness served also to evoke the spiritual and philosophical currents which gave voice to "Samson Agonistes," "Paradise Lost" and "Paradise Regained." No less can we omit the deformities of Byron, Hawthorne, Steinmetz, a Pasteur, a Scott, in appraising the character of their creative endeavors.

Syphilis has also played its part in harassing the genius to articulation. Reaching its final stage in Nietzsche, it is responsible for the terrible brilliance of his "Zarathustra". And to its incursions may well be laid many of the passionate utterances of a Verlaine, a Beaudelaire, a Heine. At times the genius is aroused to cynical and irascible protest in his work against the prodding of disease–Sam Johnson against his scrofula; Molière against his lifelong need of recourse to doctors, who for him "know the Greek names of all diseases, how to define and classify them, but of curing them know nothing at all." He found some measure of vindicative satisfaction in "La Malade Imaginaire" and other of his satires. An entire list of artists, even while they painted the world's great treasures, also suffered the constant encroachments of disease – among them Botticelli, Leonardo, Dürer, Georgione, Van Gogh, El Greco, and many more.

As for insanity and genius, they have so often been fellow-travelers that Lombroso and others mistakenly identified them, one for the other. However, it is rash for those of us "who pass for sane," to pronounce judgment upon the dwellers of a borderland into which we ourselves cannot adventure, and which may finally prove to be a region of larger reality. Is it insanity that dictates Coleridge's "Kubla Khan?" At what point does Rousseau, the genius "born dying," who changed the thinking of an epoch, transcend the limits of the rational? And where shall we draw the tenuous line between the seen and unseen which were such verities to a Tasso, a Blake, a Lamb, a Swedenborg, a Joan of Arc, a

Chateaubriand, a Swift, a Doctor Pevsici, and even a Christopher Columbus?

Certainly in this province of man's intellectual and spiritual creations, as they are affected by disease, we reach the most intriguing and challenging phase of our thoughts about disease's influence on man's history. Genius itself remains perhaps the most elusive of human phenomena, and in the few examples we have cited of its relation with disease, we perceive that it can effect its own alchemy. Here is an agent —disease—which works havoc in the thinking and performance of average men; when it is brought into contact with the philosopher's stone called genius, a transmutation is effected. Genius reins even this agent of dissolution for its ends. Here for the first time we see disease, if not conquered, at least foiled or tamed. This metamorphosis of disease from enemy to benefactor should provide a theme of endless fascination and instruction for the student; and the few, perhaps obvious, examples we have cited may provide a point of departure.

Suffice it to say, we here again become aware that the protagonist of our sketch is always among us. Timeless and unwearied he walks through centuries, associates with geniuses and fools; kings and beggar —thus far, with war the only constant in the continually changing pattern of life.

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And now, in closing this cursory study of disease and its influence on man's history and destiny, let us take a final glance at the entire picture. Earlier in this study, in our discussion of plagues and epidemics, we paused at the dawn of the Modern Age. By this, let it not be deduced that we have left plague or epidemic there behind us. Alas, not so! While humanity has learned, since those early centuries, to travel at great speed, it has never been quite fast enough to outdistance Disease. He is always at our shoulder, if not indeed ahead of us.

True, the Black Death has disappeared—but this was not of our own doing. It spent itself; in fact, as an added sop it seems to have carried along with it Europe's leprosy. Since that day we have had our epidemics. Of most recent memory is the great Pandemic of 1918, which revealed modern man as helpless on occasion as mediaeval man. World War I also disclosed that, despite our advances, we still do not entirely know how to by-pass the enemies which waylay our armies. True, our

western fronts in this war were saved by maximum precautions. However, in the Serbian, Russian and other eastern armies, typhus, unimpeded, accomplished its ravages as relentlessly as in Mediaeval wars. From 1918-1922 an estimated twenty to thirty millions of cases of typhus occurred with 10 per cent fatalities. Lenin, as Dr. Sigerist reminds us, regarded this as his first enemy—and remarked that "either socialism would defeat the louse or the louse would defeat socialism." World War II has provided another critical test of our progress with results indicative of surprising improvement.

All this may make modern man pause in his over-confidence. This is not to say that we have not made progress in our struggle against disease, nor that we are without victories to our credit. For one thing, we have learned better to insulate ourselves, through quarantines, sanitary and immigration laws, so as to lessen the danger of epidemic. For another thing, we have discovered new prophylaxes and cures against some of the most persistent of our diseases.

We have learned and begun to practice what the Middle Ages overlooked; that sanitation or the lack of it and subnormal standards of life have a direct influence on the spread of disease. We now understand that disease is no metaphysical matter—it is connected with man's way of life. This is the lesson which even royalty of our earlier centuries never wanted to learn. Thus, the courts of Louis XIV or Elizabeth—at this distance—seem dazzling in luxury and grandeur. However, modern man venturing into them would not find them to his olfactory or visual liking, we are sure. Fragonard, Watteau and Gainsborough charitably omitted from their paintings numerous realistic details. This enhances their beauty but eliminates them as documentary evidence for our purposes. More truthful are the words of a Ben Johnson as he reproaches the pock-marks which were almost universal; "Could there not be one beauty in an age and free from thee?" Closer to truth, also, is Mme. de Montespan's farewell shaft at Louis XIV, indelicate but frank, which gives us light on his personal habits. Modern man, at least, has learned pleasanter ways of living—and thereby has exposed himself less to the diseases of filth.

Perhaps the greatest victory over disease has been in the extension of man's life expectancy. In the Fifteenth Century, the child could have expected to live from twenty to twenty-five years; today we have extended his hope to sixty. As Peyton Rous says, however, we have

saved man from the diseases of childhood. We still have not removed him from attacks of cancer, high blood pressure, heart ailments and other diseases of middle age. However, it is a signal victory, to have eliminated much of the waste of human forces which comes from early death. Thus the potential leader, genius, or even artisan, may contribute his full life's labors to the sum total of man's necessities.

One of the most significant advances is in the practices of the medical profession itself. As we scrutinize our present medical world, in contrast to its mediaeval counterpart, we take reasonable satisfaction in new professional attitudes. It is to be expected that medicine will never again have recourse to the expedients to which it once, not too long ago, resorted; amulets, incantations and the strange witch's brews, which passed for respectable Materia Medica. Doctors today evidence a greater humanity than their predecessors who virtually flayed their patients into cure or death. Early chronicles indicate that frequently the speedy death in an auto-da-fe was preferable to the solicitudes to which Middle Age doctors subjected their patients. The horrible inquisition to which even royalty was subjected in its fight against death is evidenced in an illuminating account, quoted by Haggard, of Charles II's bitter final hours. Having fallen into a convulsion, due it is believed, to an embolism, the king was put through a series of bleedings, blisterings, emetics, purgatives, plasterings, combined with so repugnant a succession of medicines, including drops of human skull, as would have killed a well man, and did certainly accomplish for Charles what the embolism began, but with added discomfort. As a Seventeenth Century physician, John Ward, writes in his diary, "It may be said of some physicians that they cure their patient, as Nero did his senators, by cutting their veins, or rather their throats."

True, these victories do not seem too many. Nevertheless, they indicate progress. Even more, they give hope. For within the accelerated speed of the past century, medicine has covered greater ground than in the forty centuries which preceded it. On this advance, medical leaders base their belief that humanity may yet reach that Elysium in which disease will no longer prey on mankind.

For the present, however, Disease still stands relentlessly barring our way. We shall have to wrestle with him often and fiercely before the final conquest. Hence for today victory must lie in the struggle itself. And there is indeed signal inspiration in the fact that men today,

more than ever, are expanding selfless days and nights in unquiet and determined search, to release their fellows from this ravager. Like the true man of Carlyle, for whom self-abnegation and perpetual labor are allurements, these scientists are narrowing the province of disease's insatiable predations. By illuminating the great mystery of the human complex, they are arming man with self-knowledge—the surest weapon to cope with his ubiquitous enemy. Thus they are gradually giving design to life and a purposefulness to history. But modern man, no less than his progenitors, still faces the age-old challenge; the conquest of war and disease. They are still the supreme tests, still the witnesses to his failure thus far. On his eventual ability to conquer them lies his vindication. Is he forever to remain only the helpless instrument of forces which constantly buffet him about? Or is he to emerge at last, in possession of his full powers, the wilful master of his destiny?

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SECTION ON MICROBIOLOGY

MAY 19, 1948

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I. EXECUTIVE SESSION

a. Reading of the Minutes

b. Election of Section Officers
For Chairman—Gregory Schwartzman
For Secretary—Harry Most

c. Election of five members of the Advisory Board
Frank L. Horsfall, Jr. (1948-9)
Colin M. MacLeod (1948-50)
John G. Kidd (1948-51)
Rene J. Dubos (1948-52)
Ralph S. Muckenfuss (1948-53)

II. PAPERS OF THE EVENING

a. Studies on the mechanism of polysaccharide inhibition of virus multiplication
Harold S. Ginsberg (by invitation) and Frank L. Horsfall, Jr.
Hospital of the Rockefeller Institute

b. Stability of bacterial viruses in solutions of salts
Mark H. Adams, Ph.D. (by invitation)
New York University College of Medicine

c. Dextran-forming streptococci from the blood in subacute endocarditis and from the throats of healthy persons
Edward J. Hehre (by invitation)
Cornell University Medical College

d. Effect of nucleic acids and carbohydrates on the formation of streptolysin
Alan W. Bernheimer, Ph.D. (by invitation)
New York University College of Medicine

e. Treatment of amebic hepatitis with chloroquine
Neal J. Conan (by invitation)
New York University College of Medicine

Studies on the Mechanism of Polysaccharide Inhibition of Virus Multiplication

HAROLD S. GINSBERG (by invitation) and FRANK L. HORSFALL, JR.

From the Hospital of The Rockefeller Institute for Medical Research

It was demonstrated recently[1, 2, 3] that type specific capsular polysaccharides of Friedländer bacilli alter the course of infection with PVM and mumps virus. Multiplication is inhibited when polysaccharide is injected as long as 4 days after inoculation of either virus in appropriate hosts. Polysaccharide does not inactivate or demonstrably alter the virus, nor is a virus-polysaccharide combination formed. Present evidence indicates that polysaccharide does not block virus "receptors" of host cells and even in the presence of large quantities of carbohydrate virus is adsorbed by host tissue thereby completing the first step in infection.

The capsular polysaccharide of Friedländer bacillus type B (Fr. B) does not inhibit multiplication of influenza A, influenza B and Newcastle disease viruses[2] which multiply rapidly. This suggested that the latter viruses may require different metabolic systems within the susceptible cells of appropriate hosts than do mumps virus and PVM which increase in concentration at a slower rate.

The viruses of influenza A, influenza B and Newcastle disease interfere with the multiplication of each other.[4, 5, 6] If these viruses did require host metabolic systems different than mumps virus and PVM for multiplication, it seemed possible that the former viruses would not interfere with the multiplication of the latter. Experiments were carried out to test this hypothesis.

Varying quantities of mumps virus were inoculated into the allantoic sac of chick embryos, and followed in 4 days by inoculation of varying quantities of the PR8 strain of influenza A or the Lee strain of influenza B virus. After a further period of 2 days, the allantoic fluids were removed, and their hemagglutination titers determined in the presence of a constant quantity of immune rabbit serum, either anti-mumps, anti-PR8 or anti-Lee. When quantities of influenza virus were employed, which were equal to or smaller than the quantity of mumps virus inoculated, both viruses multiplied simultaneously in the allantoic sac.

Due to the fact that the influenza virus strains employed kill chick embryos 3 to 4 days after inoculation, it was necessary to shorten the total period of incubation in order to use these influenza viruses as the first inoculum. Under these conditions, when as much as 10^6 E.I.D. of each virus was employed, simultaneous multiplication of influenza and mumps viruses was demonstrated.

Influenza A and B viruses mutually interfere in the mouse lung.[4] If the theory proposed above were correct, then PVM and influenza viruses should not interfere with the multiplication of each other in the mouse. The intranasal inoculation of PVM was followed in 4 days by the intranasal inoculation of a similar quantity of PR8 or Lee virus. After a further interval of 2 days the mouse lungs were removed, and appropriate procedures carried out to determine the presence of PVM and influenza viruses by the hemagglutination technique. In each instance there was simultaneous multiplication in the mouse lung of influenza viruses and PVM. In order to carry out experiments in reverse order, strains of influenza A and B viruses which had not been "adapted" to the mouse were employed.[7] When either the FM1 strain of influenza A virus or the B1103 strain of influenza B virus preceded the intranasal inoculation of PVM by 2 days, it also was found that influenza viruses did not interfere with the multiplication of PVM.

Due to the lack of a common host it was not possible to determine whether PVM and mumps virus mutually interfere, as theoretically they should. Present evidence suggests that mumps virus and PVM require different host metabolic systems for multiplication than the viruses of influenza A, influenza B, and Newcastle disease. This may afford an explanation for the fact that Fr. B inhibits the multiplication of mumps virus and PVM, but fails to alter the course of infection with the influenza-Newcastle group of viruses.

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*Dextran-Forming Streptococci from the Blood in Subacute Endocarditis and from the Throats of Healthy Persons**

EDWARD J. HEHRE

Department of Bacteriology and Immunology, Cornell University Medical College

Through the action of various bacteria or of cell-free enzymes derived from them, sucrose can be converted into *dextrans* (glucose polymers), or *levans* (fructose polymers). Most streptococci do not synthesize either one of these polymers, but some non-hemolytic streptococci do form dextran, others levan, and still others mixtures of dextran and levan. Cultures of streptococci that form one or both of these polysaccharides are likely to become slimy or viscous if sufficient sucrose is contained in the medium. However, "slime from sucrose" (*i.e.*, a slimy or viscous appearance of sucrose cultures) is a wholly inadequate criterion for the presence either of dextran or of levan. Dextrans and levans are serologically reactive polysaccharides; and the application of serological tests in combination with certain chemical and physical tests furnishes a method which is adequate not only for the exact recognition of small amounts of dextrans or levans but also for the distinction of one from the other.

By use of that method, we[1] established the occurrence, in about 40 per cent of patients with subacute endocarditis, of a variety of streptococci that produces abundant dextran (but little or no levan) from sucrose. Important from the standpoint of the pathogenesis of subacute endocarditis is the question of whether or not this newly recognized variety occurs in the throats of healthy people. With Dr. Dorothy Genghof, we examined cultures of bacteria isolated from the throats of 18 healthy young adults with no history of recent respiratory illness. Material from the pharynx was streaked on plates of fresh beef infusion agar enriched with horse blood, yeast extract and glucose; the plates were incubated for 2 days at 37° C either aerobically or, more frequently, in an anaerobic jar; from 50 to 70 isolates per person were obtained and tested for capacity to synthesize dextran or levan by the previous method.[1]

Of the 1096 cultures tested, 296 formed levan, either alone or in mixture with dextran; 20 representative strains of these bacteria had taxonomic features typical of *Streptococcus salivarius*. Twenty-eight strains, obtained from the throats of 9 of the 18 subjects, produced abundant dextran but little or no levan. The supernatant fluids of sucrose broth cultures of those strains showed turbidity on treatment with 1.2 volumes of alcohol, and precipitation in dilutions from 1:100 to 1:40,000 *vs.* a dextran-reactive type 2 pneumococcus antiserum, whereas the fluids of glucose broth cultures of the same strains gave negative results; the absence of levan was shown by the failure of the sucrose broth culture fluids to give serological precipitation in dilution from 1:10 to 1:1000 with a potent levan-reactive antiserum, or to show any detectable amount of chemically determined polyfructoside.

The 28 dextran-formers isolated from throats had taxonomic features like those previously described for the dextran-forming streptococci from endocarditis.[1] Their colonies on 5 per cent sucrose agar were small when incubated aerobically; they had the capacity to oxidize hemoglobin and, usually, to produce ammonia from arginine and acid from inulin; and they failed to produce acid from xylose or starch. Twenty of the strains were identical in those properties. These taxonomic features are similar to the description for *Streptococcus s.b.e.*, which Loewe, Plummer, Niven and Sherman[2] isolated from the blood of endocarditis patients. These authors did not recognize

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the immunochemical feature of dextran formation in their original paper[2] that appeared simultaneously with our publication,[1] but they later reported[3] that sucrose broth cultures of most strains of *Streptococcus s.b.e.* have a viscous or slimy appearance. The same authors, however, maintain[2, 3] that *Streptococcus s.b.e.* is absent from the normal human throat.

Our dextran-forming streptococci seem to constitute a group closely similar to the *Streptococcus s.b.e.* However, since their exact relationship has not been determined, it seems desirable to apply the tentative term *Streptococcus DS* to our group of strains because the production of dextran from sucrose was used as the primary criterion for setting up the group. As shown in this paper, although present apparently in much smaller numbers than *Streptococcus salivarius,* streptococci of the *DS* variety do occur in the throats of healthy persons and, hence, may be regarded as a part of the normal flora of the human throat as well as one of the important agents of subacute bacterial endocarditis.

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Stability of Viruses in Solutions of Salts

MARK H. ADAMS

Dept. of Microbiology, New York University, College of Medicine

A series of seven coli-dysentery phages were tested for their relative stabilities in broth and in 0.1 N sodium chloride. In all cases the viruses were much more stable in broth than in saline, the most marked difference being with phage T5. This phage is inactivated in accordance with the kinetics of a first order reaction, the half life in saline at 37°C being less than a minute. In broth the phage must be heated to 70°C before the velocity of inactivation reaches this magnitude.

The stability of phage T5 in saline could be increased by adding various divalent cations at 10^{-3} M concentration. Of these, barium, strontium, calcium, magnesium, manganese, cobalt, nickle, zinc, cadmium and copper all had a marked protective effect, while lead and mercuric ions did not protect the phage. The protective effect of magnesium ion against inactivation of phage T5 in saline was titrated over a considerable range of concentrations and temperatures. At 10^{-5} M magnesium ion the protective effect was barely detectable but at 6×10^{-2} M magnesium ion the phage was as stable as in broth and further increase in magnesium ion concentration did not further increase phage stability. The first order velocity constants of inactivation at constant temperature varied with the second power of the magnesium ion concentration.

Similarly increasing the sodium ion concentration from 0.1 N to 1.0 N resulted in a tremendous increase in phage stability, the first order velocity constants increasing with the eighth power of the sodium ion concentration.

Ammonium ion also had a protective effect against the inactivation of phage T5 in saline. Various anions tested such as chloride, sulfate and phosphate had no effect either protective or destructive on the in-

fectivity of phage T5. Citrate and oxalate ions accelerated the rate of inactivation of phage T5 to an extent which could be explained on the basis of complex formation with traces of divalent metals. The citrate complexes of calcium and magnesium for instance did not protect phage T5 from inactivation as did the metallic ions alone.

The simplest explanation of these results would seem to be that phage T5 can form complexes with a number of cations, and that the infectivity of these complexes is much more stable than that of the free virus.

* * *

The Treatment of Amebic Hepatitis with Chloroquine

NEAL J. CONAN, JR.

From the Department of Medicine, College of Physicians and Surgeons Columbia University, and the Presbyterian Hospital, New York

The wartime antimalarial drug research program disclosed a number of highly active 4 aminoquinoline compounds of high activity. It seemed logical to determine whether their antiplasmodial activity extended to other pathogenic protozoa. Because more pharmacological information was available concerning chloroquine, 7 chloro -4- (4-diethylamino -1- methylbutylamino) quinoline, it was decided to test this drug against Endameba histolytica, an infection prevalent in the New York area. Since this drug is localized within the livers of various animals, and presumably man, to some 500 times its plasma concentration, and since only about 8 per cent of the oral dose appears in the feces, it appeared a priori that amebic infection of the liver rather than of the colon would be the test object of choice.

Preliminary results published previously indicated: 1) That chloroquine possesses in vitro activity comparable to that of emetine and superior to that of Anayodin and Carbarsone, 2) That it is more effective in amebic hepatitis than amebic colitis, and 3) that in daily doses of 0.3 gm of the base for two or three weeks no significant drug toxicity occurred.

To date, chloroquine has produced symptomatic and parasitological cure of 16 out of 31 cases of amebic colitis, and a prompt clearing of signs, symptoms and abnormal liver function tests in twelve cases of amebic hepatitis. This report presents detailed observations concerning six of these cases, four of which were studied at the Presbyterian Hospital, one at the Bronx Veterans Administration Hospital, and the other at the Hospital for Tropical Diseases, London, the data of this case being supplied through the courtesy of Drs. F. Murgatroyd and N. H. Fairley. The other 6 cases were studied by Dr. Howard B. Shookhoff of the Tropical Disease Diagnostic Service at the Columbia-Presbyterian Medical Center.

In the 6 cases reported here, 6 had enlargement and tenderness of the liver, 5 had fever of sigfinificant degree (102°F. or higher), Endameba histolytica was demonstrated in the feces of 5 and in pus draining from a liver abscess in one, four had involvement of the right diaphragm as manifested by splinting and pleural effusion. There was abnormal retention of Bromsulfthalein in the four cases in which this test was performed, and elevation of the serum alkaline phosphatase in two of five cases in which it was measured. The cephalin-cholesterol flocculation test was negative in the 5 cases in which it was performed.

Under treatment with chloroquine there occurred in each instance within two to four days definite improvement in all the aspects of the clinical and laboratory pattern. All patients regained their previous health and have maintained it over periods of from 2 to 15 months since discontinuation of therapy.

In two instances a comparison has been

afforded between chloroquine and emetine. In one case emetine produced a favorable but incomplete response inasmuch as one month after there remained low grade fever, enlargement and tenderness of the liver as well as anorexia, nausea and failure to gain weight, within a week of treatment with chloroquine all of these manifestations disappeared. The other is the case of Drs. Murgatroyd and Fairley in which there was a draining liver abscess in the pus of which Endameba histolytica were demonstrated throughout various treatment regimes including emetine parenterally, orally and locally by irrigation. The amebae disappeared from the liver pus on the fifth day of chloroquine treatment and the wound was healed by the twelfth day.

Chloroquine would thus appear to be a safe and effective substitute for emetine in the treatment of extraintestinal amebiasis. Its lack of serious toxic potentialities render it preferable to emetine. When coupled with a superior intestinal antiamebic drug it should permit complete therapy of any amebic infection on even an ambulatory basis if the condition of the patient warrants it.

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Effect of Nucleic Acids and Carbohydrates on the Formation of Streptolysin S.

ALAN W. BERNHEIMER, Ph.D.

Department of Microbiology,

New York University College of Medicine

Yeast nucleic acid stimulates the formation of a potent hemolysin in cultures of *Streptococcus pyogenes* (Okamoto, H., Jap. J. Med. Sci., IV. Pharmacol., 1939, 12, 167). The properties of the hemolysin indicate that it is probably identical with streptolysin S. It has been found that little or no streptolysin S is formed in chemically defined-medium cultures unless the medium is supplemented with two other factors. Neither one of these factors is needed for growth but both are required for streptolysin S formation. The chemical nature of each has been elucidated and pertinent information concerning them follows:

The first factor is supplied by ribonucleic acid from yeast, wheat, mammalian liver, or streptococci, but apparently not by ribonucleic acid from tobacco mosaic virus nor by desoxyribonucleic acid prepared from several sources, nor by purine- and pyrimidine-mononucleotides or their hydrolysis products. Fractionation of yeast nucleic acid, following enzymatic splitting, has yielded a polynucleotide whose streptolysin-inducing activity is approximately 100 times that of yeast nucleic acid. The polynucleotide has been partially characterized but knowledge of its exact composition is incomplete.

The other factor is present in peptone and in muscle. It can be replaced by minute amounts of maltose or by somewhat larger amounts of glucosamine or trehalose. As little maltose as M/64,000 is sufficient to cause a significant degree of streptolysin formation. Glucose as well as many other mono-, di- and polysaccharides, are either inactive or active only in relatively high concentrations.

When appropriate concentration of polynucleotide, maltose, and glucose are used, streptolysin S can be produced in a medium the chemical composition of which is essentially defined. Using this information, a satisfactory method of producing streptolysin S in mass cultures has been developed.